

**AVEED™ (TESTOSTERONE UNDECANOATE) FOR  
TESTOSTERONE REPLACEMENT FOR TREATMENT  
OF HYPOGONADISM**

**BRIEFING DOCUMENT FOR JOINT MEETING OF  
REPRODUCTIVE HEALTH DRUGS ADVISORY COMMITTEE  
&  
DRUG SAFETY RISK MANAGEMENT  
ADVISORY COMMITTEE**

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

<b>Abbreviation</b>	<b>Definition</b>
ADR	Adverse drug reaction
AE	Adverse event
AIT	Allergen immunotherapy
BHP	Benign prostatic hypertrophy
BMD	Bone mineral density
BMI	Body mass index
CAD	Coronary artery disease
C <sub>avg</sub>	Average concentration
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C <sub>max</sub>	Maximum concentration
CT	Computed tomography
EHR	Electronic health record
EU	European
EU-RMP	EU-Safety Risk Management Plan
FDA	Food and Drug Administration
HCP	Healthcare provider
IM	Intramuscular
ISS	Integrated Summary of Safety
IV	Intravenous
JMO	Japanese Maintenance Organization
MedDRA	Medical Dictionary of Regulatory Activities
MSSO	MedDRA Shared Services Organization
NDA	New Drug Application
PK	Pharmacokinetics
POME	Pulmonary oil microembolism
PT	Preferred term
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious adverse event
SCIT	Subcutaneous immunotherapy
SD	Standard deviation
SMQ	Standardised MedDRA Query
TRT	Testosterone replacement therapy
TU	Testosterone undecanoate

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<b>Abbreviation</b>	<b>Definition</b>
URT	Upper respiratory tract
US	United States
WHO	World Health Organization

## 1. EXECUTIVE SUMMARY

### 1.1. Introduction

AVEED™ is a depot formulation of testosterone undecanoate (TU) indicated for long-term testosterone replacement therapy (TRT) in hypogonadal men.

In adult males with conditions associated with a deficiency or absence of endogenous testosterone, intramuscular (IM) administration of 750 mg AVEED maintains eugonadal testosterone concentration (300-1000 ng/dL) for up to 10 weeks. Following baseline administration of 750 mg, a second 750 mg dose is given at 4 weeks followed by 750 mg every 10 weeks thereafter.

AVEED (750 mg TU/3 mL) is the same formulation as Nebido® (1000 mg TU/4 mL) which is approved in 94 countries (including the European Union). The treatment regimen approved in rest of world is 1000 mg TU given at 10- to 14-week intervals with an optional dose given 6 weeks after the first dose. Nebido has been approved for worldwide use for over 9 years, and since its launch in 2003 through November 24, 2011, more than 3.1 million doses of Nebido have been sold, providing extensive postmarketing safety experience. In addition, safety data from 18 clinical trials conducted in 3,556 subjects treated with TU is available.

Key benefits of AVEED are (1) extended dosing interval of 10 weeks, (2) efficacious with 94.0% of subjects achieving a  $C_{avg}$  within the eugonadal range, (3) no risk of transference (unlike class labeling for all topical TRTs), and (4) mean testosterone levels not exceeding supraphysiological concentrations (unlike short acting injectable TRTs).

In 2009, the Food and Drug Administration (FDA) issued a complete response letter stating AVEED could not be approved due to FDA's concern regarding 2 types of immediate post-injection reactions. These reactions consisted of an acute coughing episode immediately after injection. The reaction is thought to be caused by oil from the injection entering the blood stream and reaching the lung. This event is known as pulmonary oil micro-embolism, or by the acronym "POME." FDA was also concerned about immediate post injection reactions that included clinical features consistent with anaphylaxis.

Immediate post-injection reactions are reported with short-acting injectable TRTs. The labels for both testosterone enanthate and testosterone cypionate list anaphylactoid reactions on their package inserts among observed adverse reactions. There are 2 studies in the literature in which short-acting injectables were used that noted post-injection cough at rates between 1.5 in 100 and 1 in 1000.(1,2)

Endo provided a New Drug Application (NDA) resubmission which presented additional data from a review of the clinical and postmarketing databases to identify and characterize all cases of POME and anaphylaxis. In addition to Endo's adjudication of potential POME and anaphylaxis cases, an adjudication of potential POME and anaphylaxis cases by 2 independent adjudicators has been submitted to the FDA. These reviews were conducted to better assess the true rate of these post-injection reactions.

This briefing book provides a summary of the effectiveness and general safety experience with AVEED in clinical development and the safety experience reported in postmarketing with TU. Additional sections provide detailed findings from an independent adjudication of POME and anaphylaxis. Based on the independent adjudication, the rate of POME in the clinical studies was 1.5 cases (95% CI, 0-3.2) per 10,000 injections,<sup>1</sup> and the reporting rate of POME in the postmarketing database was 0.7 cases (95% CI, 0.6-0.8) per 10,000 doses sold. The rate of anaphylaxis in the clinical studies was 0 cases (95% CI, 0-10.4) per 10,000 patients,<sup>2</sup> and the reporting rate of anaphylaxis in the postmarketing database was 0.4 cases (95% CI, 0.3-0.5) per 10,000 patients.

Finally, the briefing book concludes with a proposed risk management plan and an overall benefit risk assessment to support the approval of AVEED.

## **1.2. Medical Need in Men with Androgen Deficiency**

### **1.2.1. The Condition of Male Hypogonadism**

The Endocrine Society defines hypogonadism in men as “a clinical syndrome that results from failure of the testis to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa due to disruption of 1 or more levels of the hypothalamic-pituitary-testicular axis.”<sup>(3)</sup>

The clinical presentation of hypogonadism in men depends on the age of onset of androgen deficiency.<sup>(3)</sup> Prepubertal onset of hypogonadism presents with eunuchoidism, delayed development of secondary sex characteristics, and high pitched voice. In adult men (postpubertal), symptoms and signs are nonspecific and depend on many factors including age of onset and duration of the androgen deficiency. Signs suggestive of androgen deficiency include loss of body (axillary and pubic) hair, reduced sexual desire, reduced libido, breast discomfort, gynecomastia, shrinking testes, low trauma fracture, low bone mineral density (BMD), hot flushes, and sweats.

Other, less specific signs and symptoms include decreased energy and motivation, depressed moods, poor concentration and memory, sleep disturbance, mild anemia, reduced muscle bulk and strength, increased body fat and body mass index (BMI), and diminished physical or work performance.

The threshold testosterone level below the normal range at which symptoms of androgen deficiency and adverse health outcomes occur is not precisely defined. Based on the Endocrine Guidelines, for most symptoms, the average testosterone threshold corresponded to the lower limit of normal range for young men (~300 ng/dL).

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<sup>1</sup> POME rates are reported per injection since the risk appears to be related to the injected material entering the vasculature with each injection (technique based).

<sup>2</sup> Anaphylaxis rates are reported per patient since the risk is based on the patient’s immune system recognizing the injected material (recipient related).

### 1.2.2. Benefit of Testosterone Replacement Therapy

The Endocrine Society recommends replacement therapy for symptomatic men with classical androgen deficiency to induce and maintain secondary sex characteristics and to improve BMD, sexual function, sense of well-being, and muscle mass and strength.(3) The Endocrine Society recommends against a policy of offering testosterone therapy to all older men with low testosterone levels. Therapy should only be offered on an individual basis due to the uncertainty about the risk and benefits in this age group.

The guidelines also recommend evaluating patient 3 to 6 months after treatment initiation and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering any adverse effects, and to check compliance. The need to monitor long term therapy is based on the difference in target organ response to testosterone. Some effects of therapy are seen early for example, effects on sexual interest whereas; changes in body composition may not be observed for 3 months or greater.(4) The effect of testosterone replacement on BMD may become detectable after 6 month and continuing up to 2 to 3 years.(5) This is reflected in the guidelines which recommend monitoring for changes in BMD after 1 or 2 years on therapy.

### 1.2.3. Testosterone Replacement Therapies

TRTs have been approved by the FDA since 1973. There are currently 5 routes of administration available including IM injection, transdermal (gels, solutions or patches), oral (not available in the United States), buccal adherent tablets, or pellets for implantation. The therapeutic target is to increase serum testosterone levels into mid normal range for healthy young men. These formulations can deliver adequate TRT, although each has unique limitations and risks.

More than 95% of hypogonadal men choose either a transdermal or IM injectable route. Most patients (≈65%) choose transdermal gel or solution formulations. Although these products, which include the 3 most recently approved TRTs, AndroGel® 1.62%, Axiron®, and FORTESTA®, achieve acceptable levels of testosterone replacement (≈77% to 87% of men maintain average daily testosterone concentrations within the eugonadal range), they require daily application, require adequate product drying time (2½ to 5 minutes) prior to getting dressed and can cause skin reactions. Most importantly, all have the potential for causing secondary exposure to women or children. The secondary exposure, or transference, can cause virilization in women and children and irreversible changes in children (eg, fusion of bone plates), which led the FDA to require Black Box warnings about transference on all of these products. The Pediatric Advisory Committee Meeting on June 23, 2009 held an expanded review of adverse events (AEs) and overview of secondary exposure of testosterone in children (labeling – black box warning/medication guide). The committee recommended measures to be taken immediately to reduce risk of exposure.

Depot testosterone formulations which are dosed IM include testosterone enanthate and testosterone cypionate. About 30% of men treated for hypogonadism use these formulations. These products are formulated in an oil-based vehicle and are administered every 2 to 4 weeks, therefore requiring 13 to 26 doses per year. They do not have the risk of transference, but like AVEED, are in an oil-based vehicle, and therefore, also carry the risk of immediate post-injection reactions like cough, respiratory distress, and anaphylaxis. These short acting injectable products have the potential to cause supraphysiological levels of testosterone.

## **1.2.4. Testosterone Undecanoate Has Benefits That Can Provide Another Option for Patients**

### **1.2.4.1. Extended Dosing Interval**

One of the key benefits of AVEED is continuous testosterone delivery over an extended period of time. The injection interval for TU, after the loading dose, is 10 weeks ( $\approx 5$  injections/year) compared with daily treatment for the topical therapies or 2 to 4 week intervals (13 to 26 injections per year) for the IM testosterone enanthate replacement therapy. Reducing dosing frequency may improve patient persistence to medication. In other therapeutic areas, it has been shown that less frequently dosed products like Boniva® (once monthly) have better patient persistence than product dosed daily and weekly.

### **1.2.4.2. Efficacious**

AVEED is efficacious with 94.0% of subjects achieving normal testosterone blood levels, defined as  $C_{avg}$  300 to 1000 ng/dL, and only 5.1% of subjects with levels below the therapeutic range ( $C_{avg} < 300$  ng/dL). Other recently approved products also used the same criteria for approval. The percentage for topical formulations ranges from 77% to 87%. Other TRT products (short-acting parenteral testosterone products and testosterone topical formulations) may require dose adjustment to achieve adequate serum testosterone levels.

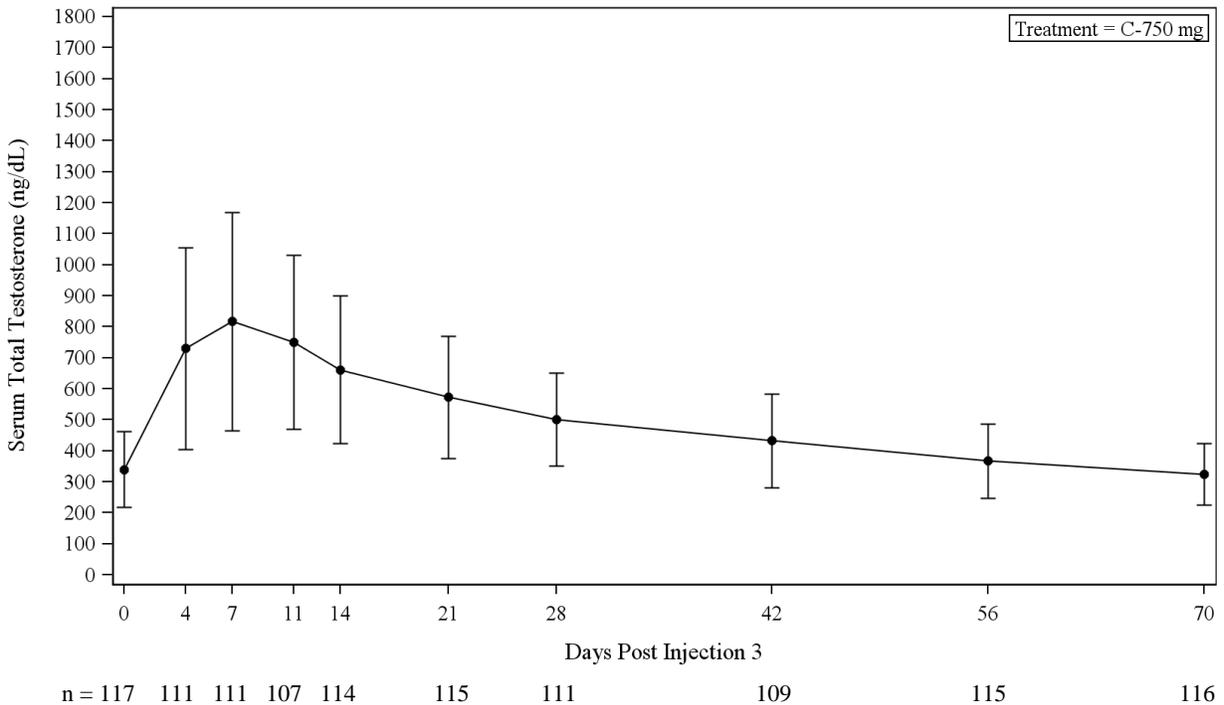
### **1.2.4.3. No Risk of Transference**

Unlike the transdermal gel formulations which are the most widely used products in the United States, there is no potential for unintended transfer of testosterone to women or children from men receiving AVEED. Even small quantities of testosterone, transferred on a repeated basis to these individuals, may result in the clinical signs and symptoms of hyperandrogenism. In women, this can manifest as virilization and in children this can manifest as enlargement of the penis or clitoris, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. In most cases, these signs and symptoms regressed with removal of the exposure to testosterone gel. In a few cases, however, enlarged genitalia did not fully return to age-appropriate normal size, and bone age remained modestly greater than chronological age. These safety concerns have resulted in the inclusion of a black box warning regarding secondary exposure on the package inserts of topical TRTs. These products also require a Medication Guide as part of the REMS. Despite the change in labeling, the black box warning, and the REMS, there continue to be reports of AEs due to transference.

### **1.2.4.4. Mean Testosterone Levels Do Not Exceed Supraphysiological Testosterone Levels**

In the Phase 3 pivotal study (IP157-001 Part C and C2), treatment with AVEED 750 mg maintained mean testosterone concentrations in the eugonadal range over 10 week dosing interval (Figure 1). In contrast, for short-acting injectable products, serum testosterone levels rise into the supraphysiological range, then decline gradually by the end of the dosing cycle (Figure 2).

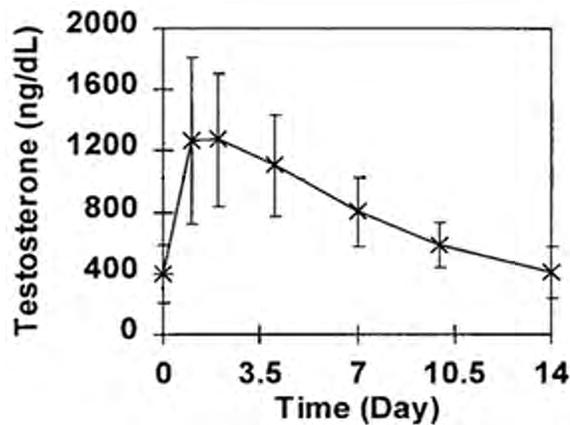
**Figure 1: Mean (SD) Serum Total Testosterone Concentrations (ng/dL) Resulting from the 3<sup>rd</sup> Intramuscular Injection of Testosterone Undecanoate**



Data Source: 5.3.5.1, Study IP157-001 Part C&D [Figure 14.2.1]

Note: C-750 mg refers to TU 750 mg.

**Figure 2: Steady-State Pharmacokinetic Profiles of Testosterone from Biweekly Intramuscular Injections of Testosterone Enanthate Measured at Week 16**



Data Source: *J Clin Endocrinol Metab.* 1999;84:3472.(6)

#### 1.2.4.5. Persistence on Testosterone Replacement Therapy

Persistence on therapy is important for confirming the diagnosis of hypogonadism and for achieving therapeutic benefit. The Endocrine Society guidelines recommend a therapeutic trial of adequate duration (3 to 6 months) to assess response to therapy. One of the challenges of

testosterone replacement with currently available products in the United States is that persistence is poor. Prescription data from the United States show that over 60% of hypogonadal men discontinue TRTs within 6 months. Only 41% of men remain on transdermal gel products and only 29% of men remain on short acting injections at 6 months (Truven Health Analytics MarketScan® database). Because of this lack of persistence with treatment in many men, it will remain unclear whether the diagnosis is accurate and in those who are hypogonadal, the benefits will not be maintained.

To understand whether the availability of a long-acting depot injectable (eg, TU) impacts medication persistence (the duration of time from initiation to discontinuation of therapy), we analyzed prescription claims data (IMS Longitudinal Prescription: LRx) from Germany where TU injection (marketed under the trade name of Nebido) has been available as a treatment option since 2004. Germany has the largest TRT volume in Europe. These data, which represent approximately 80% of the German population, are regarded as a reliable prescription claims source and are commonly used by healthcare organizations and regulatory agencies.

The data show that 26.1% of patients remained on transdermal gel products and 4.9% remained on the short-acting injectable products at 6 months (Table 1). In contrast, TU injection had a longer duration of persistence. Patient persistence was 56.2% at 6 months which is approximately 2-fold higher than that attained with the transdermal gels. This indicates that an adequate therapeutic trial of TRT can be achieved in more men on TU injection than on the other formulations.

**Table 1: Persistence of Testosterone Replacement Therapy Products Up to 2 Years – German IMS® LRx Database**

Formulation (Total Patients)	Persistence (%) in Germany IMS® LRx Database			
	90 days (3 months)	180 days (6 months)	360 days (1 year)	720 days (2 years)
Any Testosterone Therapy (n=17,385)	45.2	32.7	18.6	10.3
Transdermal Gels (n=7,609) <sup>a</sup>	39.1	26.1	12.4	5.7
Short-Acting Injections (n=4,702) <sup>b</sup>	14.7	4.9	1.6	0.5
TU Injection (testosterone undecanoate) (n=4,663)	70.1	56.2	34.7	20.2

<sup>a</sup> Transdermal Gels: Androtop gel, Testim, Tostran, Testotop

<sup>b</sup> Short-Acting Injections: Testosterone Depot, Testosterone Enanthate, Testoviron

Also shown are the observed 1-year and 2-year persistence rates of these products (Table 1). Again, persistence remained higher for TU injection than for other formulations suggesting that a greater proportion of men needing therapy will remain on therapy with TU injection.

As observed from the German data, patient persistence declines over time, similar to what was observed in the US MarketScan data. Although we cannot know exactly from the data what impact the availability of a long-acting injection option might have on the treatment of men in the US, it is not unreasonable to think that AVEED may demonstrate a pattern of persistence in the United States similar to that seen in Germany.

AVEED will also have the advantage of administration within a healthcare setting, thus confirming that the patient will be compliant. This is unlike topical gels and short-acting injectables which are dosed daily and weekly, respectively, and can be administered by the patient at home. Because patients do not always take their TRTs as directed, confirmation of the diagnosis may be lacking and, clinical benefit may not always be attained in those who need it.

#### 1.2.4.6. Summary

In summary, hypogonadism is a condition that merits TRT. All current forms of testosterone therapy have limitations and no one form is best for all men. Regardless of limitation, most patients discontinue therapy within several months. Persistence on therapy is important for clinicians to evaluate a response to treatment as well as for patients to achieve therapeutic benefit. The extended dosing interval of AVEED may contribute to the increased persistence and may make it be more favorable for patients to remain on therapy.

AVEED does not exceed supraphysiological testosterone levels like the short-acting injectables. Because of its route of administration AVEED does not carry the risk of transference, but the vehicle does carry intrinsic risks of post injection reactions similar to other injectable testosterone products. With each testosterone product having its unique advantages and disadvantages, the decision of which product to use has to be made through a discussion between the patient and his physician. AVEED offers another option with unique characteristics for the patient and physician to consider.

### 1.3. AVEED Effectiveness and Safety in Clinical Development

The AVEED formulation contains 750 mg TU in a castor oil vehicle and benzyl benzoate to extend release of testosterone undecanoate. Benzyl benzoate also increases injectability. The clinical development program was designed to identify and confirm a dosing and administration schedule that could maintain average testosterone at eugonadal concentration while having low risk for exceeding  $C_{max}$  concentration limits accepted by FDA.

FDA approval of recently marketed TRTs (Table 35) was based upon the following criteria.

- $\geq 75\%$  of patients have testosterone  $C_{avg}$  within the eugonadal range (300-1000 ng/dL), and the lower limit of the 95% CI for the percent of patients with  $C_{avg}$  within the eugonadal range is  $\geq 65\%$ .
- $\geq 85\%$  patients have  $C_{max} \leq 1500$  ng/dL
- $\leq 5\%$  of patients have  $C_{max}$  between 1800 and 2500 ng/dL
- No patients whose  $C_{max} > 2500$  ng/dL

Study IP157-001 was the pivotal US study to demonstrate effectiveness of AVEED based on the criteria above. This study enrolled hypogonadal men from the US and was designed in 5 parts (Parts A, B, C, C2 and D). Parts A, B, C, and C2 enrolled separate cohorts while Part D, evaluating subcutaneous administration, drew patients from Parts A and C in a crossover design. Part C and C2 were definitive in establishing the effectiveness of AVEED dosing at 750 mg IM at baseline, at 4 weeks and then every 10 weeks thereafter. In Part C, intensive pharmacokinetic sampling was conducted after the 3rd and 4th injections to evaluate  $C_{avg}$  and  $C_{max}$ . In part C2

intensive pharmacokinetic sampling was conducted to evaluate  $C_{max}$  after the 2nd injection (4 weeks after the first injection). The pharmacokinetic results following the 3rd injection were defined as the primary analysis. The pharmacokinetic results following the 2nd and 4th injections were supportive. It should be noted that the dose used throughout the world is 1000 mg (4 mL) while the dose proposed in the United States is 750 mg (3 mL). When this 1000 mg dose was evaluated in study IP157-001,  $C_{max}$  exceeded criteria set by FDA. Therefore, the dose was decreased to 750 mg which gave acceptable  $C_{max}$  levels.

The  $C_{avg}$  and  $C_{max}$  following the 3rd injection met the predefined criteria (Table 2). Overall 94.0% of subjects had  $C_{avg}$  following the 3rd injection between 300 and 1000 ng/dL with a lower limit of the 95% CI of 89.7%. More than 85% of subjects had  $C_{max}$  no greater than 1500 ng/dL and no subjects had values greater than 1800 ng/dL. The findings from analysis of the data during the 2nd and 4th injection interval also met the predefined criteria and are reviewed in section 5.

**Table 2: Findings in Part C of Study IP157-001 During the 3rd Injection Interval Compared to the Prespecified Criteria for Success**

Pharmacokinetic Parameter	Range (ng/dL)	Success Criterion	Findings TU 750 mg (N=117)
$C_{avg}$ (ng/dL)	300 - 1000	$\geq 75\%$ of subjects	110 (94.0%)
		The lower limit of the 95% CI of the percent of subjects meet the criterion $\geq 65\%$	(89.7%, 98.3%)
$C_{max}$ (ng/dL)	$\leq 1500$	$\geq 85\%$ subjects	108 (92.3%)
	Between 1800 and 2500	$\leq 5\%$ subjects	0
	$> 2500$	0 subjects	0

In addition to the clinical development program establishing an effective dosing regimen for TU, there was significant safety data collected. In the clinical development program for hypogonadism, 725 hypogonadal men were treated with TU at 750 or 1000 mg providing 475.5 and 957.8 person years of experience, respectively. The clinical development program for male contraception studied an additional 407 healthy men who were treated with 750 mg or 1000 mg TU and some also received other progestational agents. Additional experience was derived from 2424 hypogonadal men who were treated with 1000 mg TU (same formulation as 750 mg TU) in postmarketing surveillance studies with 78.7% having at least 5 to 7 injections for a total of 2508.3 person-years of experience.

The postmarketing experience with Nebido (identical formulation administered at 1000 mg) is significant. Through November 24, 2011, at the time of data cutoff and lock for this submission,  $>3.1$  million doses of Nebido were sold worldwide.

#### 1.4. Pulmonary Oil Microembolism

POME is a self-limited, immediate post-injection AE which occurs with oil-based substances and has been observed after IM administration of substances such as short-acting testosterone

preparations and after myelography and lymphangiography with certain oil-based radiocontrast agents. POME often presents with acute respiratory symptoms including cough, urge to cough, and/or dyspnea, as well as occasionally other systemic signs and symptoms including lightheadedness, syncope or near-syncope, nausea, and sweating. The mechanism is believed to be related to the oil-based vehicle inadvertently reaching the venous circulation, than traveling to the pulmonary microvasculature. The phenomenon was originally described in the radiology literature when oil-based radiocontrast media were used for myelography and lymphangiography. In the case of myelography, accidental introduction of radiocontrast into the bloodstream can occur during the procedure and results in symptoms of cough and visualization of the material in the lungs on chest radiographs. Similarly, in the case of lymphangiography, lympho-venous communications in lymph nodes, particularly those affected with tumor, allowed the radiocontrast to gain access to the systemic circulation with symptoms of cough, dyspnea, and chest pain and visualization of the radiocontrast on chest radiographs.

Short-acting IM-administered testosterone preparations have also been associated with the syndrome of POME. For example, in a study reported by Mackey et al, 26 men were followed over 8 months for a total of 551 injections with testosterone enanthate formulated in castor oil. Sudden onset of non-productive cough with or without faintness occurred after 1.5% (95% CI, 0.6%-2.9%) of injections.(1)

The administration of oil-based vehicles by the IM or intravenous (IV) route has been investigated in preclinical animal studies. IM administration of a vehicle containing castor oil and benzyl benzoate has been administered to rats for up to 6 months and dogs for up to 1 year. Histologic examination of lung tissue did not demonstrate any pulmonary toxicity. In one study, castor oil administered IV to dogs was well tolerated, without evidence of systemic symptoms or deaths.

Endo endeavored to characterize all immediate post-injection reactions in both the clinical trial database and the spontaneous postmarketing safety database. Endo committed to an adjudication process of case identification that would be transparent, objective and reproducible. In order to do this, 2 independent adjudicators, both pulmonologists, were engaged and asked to (a) develop a POME case definition; (b) based on this definition, create a Medical Dictionary for Regulatory Activities (MedDRA) terms-based screening search using preferred terms (PTs) designed to retrieve the subset of all potential POME cases from all records in each dataset; and (c) review the potential cases for POME. Based on the results of this adjudication, a frequency of POME in the clinical trial database and a reporting rate in the spontaneous postmarketing database could be determined.

#### **1.4.1. Pulmonary Oil Microembolism Cases Reported in the Clinical Database**

The entire clinical trial database consisted of 3,556 subjects from both clinical and postmarketing trials. Since POME is an immediate post-injection reaction, events occurring on the day of injection suggestive of POME were retrieved using the broad group of search terms identified by the adjudicators. One hundred two (102) subjects had 110 cases that occurred on the day of injection or had events missing the date of occurrence. Utilizing the case definition the adjudicators developed, they determined that there were 3 cases of POME in 3 subjects, and that

23 cases in 22 subjects (1 subject had 2 cases) were indeterminate. They felt that 84 cases in 77 subjects were not POME.

Because POME appears to have no patient specific risk factors and can occur with each injection, the risk is considered injection specific and rates are reported as cases per 10,000 injections. The extent of exposure in the TU clinical development program at data cutoff was 20,217 injections giving an incidence of 1 POME case per 6,739 injections or 1.5 cases (95% CI, 0-3.2) per 10,000 injections.

The clinical characteristics of the POME events are similar to those reported in the literature for other oil-based products. All cases had symptoms of cough and/or dyspnea. Other symptoms such as dizziness, erythema, and hypotension were reported in some of the cases. The 23 cases that were adjudicated as indeterminate were reported as hyperhidrosis (8), hot flush or flush (5), dyspnea (3), cough (3), dysphonia (2), allergic respiratory disease (1) or hyperventilation (1). The cases of cough were adjudicated as indeterminate since onset relative to injection was not known. Note that 10 of the 23 cases were either reports of hyperhidrosis (8) or hot flush (2) observed in the male contraception studies. Because time of event was not recorded, it is not known if these events occurred before or after the injection of TU. Also, these symptoms could be confounded by the administration of a second hormonal agent since most subjects also received a progestational agent in these studies.

All indeterminate cases were considered to be clinically non-serious. One (1) case of POME was considered serious. The clinically serious case was severe cough that required medical observation but no medical intervention. Of the 3 subjects adjudicated to have had a POME event, 2 were subsequently re-treated with TU. Both subjects received 4 subsequent doses with no further reports of POME. Of the 23 subjects in which the adjudication was indeterminate, 9 were subsequently re-treated with TU without further events and 1 patient experienced POME on a subsequent injection.

#### **1.4.2. Pulmonary Oil Microembolism Cases in the Postmarketing Experience Database**

Since the launch of Nebido in 2003 (which is the same formulation as AVEED but dosed as 1000 mg [4 mL] rather than 750 mg [3 mL]), over 3.1 million doses have been sold and AEs have been collected in the spontaneous postmarketing database. A search of the database with the PTs defined by the independent adjudicators retrieved 547 cases which were reviewed by the adjudicators. Utilizing the case definition they developed, the adjudicators determined 141 cases were POME cases, 324 cases were non-POME cases and 82 cases were indeterminate. Because these are postmarketing surveillance data, a more conservative approach was taken in determining a reporting rate by adding cases classified as POME and those classified as indeterminate for a total of 223 cases.

Therefore, of the 547 cases, 223 were classified as POME giving a reporting rate of 0.7 cases (95% CI, 0.6-0.8) per 10,000 doses sold. The clinical characteristics were consistent with those observed in clinical development. Of the 223 events, there were no fatalities, 25 patients were hospitalized (6 of these cases reported resolution of symptoms in the ER) and 13 were treated with epinephrine. Twenty-seven (27) were treated with other medications such as corticosteroids and antihistamines. Of these 223 POME cases, 18 were also adjudicated as anaphylaxis and 25 were adjudicated as indeterminate. Of the 13 POME cases treated with epinephrine, 6 of these

cases were also adjudicated as anaphylaxis and 2 were adjudicated as indeterminate by the adjudicators. The reporting rate of POME cases has remained low and consistent since the launch of Nebido 9 years ago (see [Table 38](#)).

The potential for POME exists with all oil-based drug products. In the AVEED clinical development program and in the postmarketing experience, POME has been reported in the immediate post-injection period at a low rate. The majority of events were characterized as cough, urge to cough, or dyspnea. In most cases, patients were observed and no treatment was necessary. In a few patients, where the symptoms also were consistent with anaphylaxis, treatments (epinephrine, corticosteroids, antihistamines) were administered. All patients recovered without sequelae and no patients died.

## 1.5. Anaphylaxis

Anaphylaxis is a rapid-onset, hypersensitivity syndrome which can affect multiple organ systems. Although no cases of anaphylaxis were reported by the investigators in the clinical studies, cases consistent with anaphylaxis were noted in spontaneous postmarketing reports with Nebido; therefore, a comprehensive retrospective review of anaphylaxis in the clinical and postmarketing experience was performed. The 2 independent adjudicators who reviewed cases for POME, also reviewed and adjudicated the clinical and postmarketing databases for cases of anaphylaxis. A 2-step process was employed with the first step being a broad search of the clinical and postmarketing databases for potential cases of anaphylaxis followed by an in depth clinical review of the potential cases versus a case definition of anaphylaxis. The broad search used the preferred terms from the Standardised MedDRA queries (SMQs) for anaphylaxis and anaphylactic shock. These SMQs, which were not developed specifically for this evaluation but are used industry wide, were developed by a collaboration of academic, industry and regulatory groups to facilitate searches of safety databases. For anaphylaxis, the SMQ is very broad and given the syndromic nature of the process requires further review via a case definition. The case definition (criteria) that the FDA requested to be applied was outlined at the 2006 Symposium on the Definition and Management of Anaphylaxis sponsored by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network,<sup>(7)</sup> and is commonly referred to by the senior author's name, the Sampson criteria.

The Sampson criteria were developed to standardize the diagnosis of anaphylaxis. The intended goal was to develop diagnostic criteria to provide the emergency responder or treating physician with a relatively simple and rapid means to diagnose anaphylaxis. Taking the original goal of the symposium into consideration, the Sampson criteria applied to clinical studies are sensitive, but less specific for anaphylaxis compared to expert clinical review not using pre-set criteria.<sup>(7)</sup> The diagnostic criteria are based in part on whether or not there is exposure to a known allergen and the presenting signs and symptoms. Adjudication versus the Sampson criteria ([Table 31](#)) is based on whether the patient has a sensitivity to the inciting agent (allergen), the time of onset of the symptoms, and the organ systems affected by the symptoms (eg, skin/mucosa, respiratory, cardiovascular and gastrointestinal), but does not factor in the intensity of the symptoms. The criteria were developed for prospective recognition of cases by a treating physician. However, in this situation where the criteria are being applied retrospectively, cases can be adjudicated as anaphylaxis by the Sampson criteria, yet are so mild that they would not have been treated or

might not even have been recognized by the clinician as anaphylaxis at the time they were occurring.

The experts adjudicated the cases as yes, no, or indeterminate. In the few instances where there was lack of concordance between the 2 adjudicators, Endo took the more conservative assessment of the 2.

### **1.5.1. Anaphylaxis Cases Reported in the Clinical Database**

No cases of anaphylaxis were identified by the principle investigators during the course of the clinical studies; however, a retrospective post-hoc analysis of the clinical trial database was performed. Across the 3,556 subjects in the clinical development database with exposure to TU, 25 cases<sup>1</sup> occurring on the day of injection were retrieved by the PT search. Since anaphylaxis typically manifests within 30 minutes of an injected allergen exposure, only cases that occurred on the day of injection were retrieved for evaluation. Of these, none (0) were adjudicated as anaphylaxis based upon the Sampson criteria, giving a rate of anaphylaxis of 0 cases (95% CI, 0-10.4) per 10,000 patients (0 cases [95% CI, 0-8.7] per 10,000 patient-years).

The cases were only recognized as anaphylaxis after retrospective review. The symptoms resolved spontaneously and did not require therapy or hospitalization.

### **1.5.2. Anaphylaxis Cases in the Postmarketing Experience Database**

The postmarketing database which contains AEs that have been reported during the 9 years that Nebido has been marketed was searched for cases containing the anaphylaxis PTs. The search retrieved 331 cases which were reviewed. Of these, 19 cases were adjudicated as anaphylaxis (“yes”) based upon the Sampson criteria. An additional 26 cases were adjudicated as being indeterminate. Because the postmarketing reports may lack clinical detail which could hamper adjudication, a conservative approach was taken and the cases adjudicated as indeterminate were also considered as if adjudicated as yes. Therefore, a total of 45 cases were adjudicated as anaphylaxis. The reporting rate was therefore estimated as 0.4 cases (95% CI, 0.3-0.5) per 10,000 patients (0.6 cases [95% CI, 0.4-0.8] per 10,000 patient-years). Narratives of the 19 cases adjudicated as anaphylaxis are provided in [Appendix 3](#) and narratives for the 26 cases adjudicated as indeterminate for anaphylaxis are provided in [Appendix 4](#).

The onset of symptoms was reported for 31 of the 45 cases, and was within 30 minutes of injection for all 31 of the cases. The majority of these cases had characteristics of a mild reaction. Overall, there was no report of any therapy for 24 of the cases (53%), 8 cases received epinephrine, and 13 did not receive epinephrine but did receive steroids or antihistamines. Ten (10) of the cases were seen in an emergency room or were admitted to a hospital. There were no sequelae or deaths reported from these anaphylactic reactions.

The symptoms of anaphylaxis can overlap with the symptoms of POME. Cough can be a symptom of anaphylaxis and is a defining symptom of POME. Of the 45 cases adjudicated as anaphylaxis, 43 were also adjudicated as POME. When the cases adjudicated as anaphylaxis (N=45) and POME (N=223) are considered separately, there are 268 cases, but because of the

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<sup>1</sup> A case is 1 or more AEs starting on the same day, which match 1 or more of the AEs on the list of PTs for anaphylaxis.

overlap there are actually only 225 unique cases. Clinical findings associated with coughing, such as flushing, may have resulted in some POME cases to be adjudicated as anaphylaxis.

## **1.6. Proposed Risk Evaluation and Mitigation Strategy (REMS) and Additional Risk Management Interventions**

Endo takes the risk of immediate post-injection reactions associated with AVEED seriously. The proposed REMS and additional risk management interventions for AVEED have been designed to implement measures that will mitigate and control the main elements of risk. Endo will monitor and assess the components of the REMS and additional risk management interventions on an ongoing basis to ensure that they are appropriate and achieving their purpose.

Immediate post-injection reactions with AVEED are infrequent, detectable, and manageable. The proposed REMS and additional risk management interventions will:

- Educate healthcare professionals (HCPs) and patients on the risks of AVEED
- Control the circumstances around the administration of the drug to enhance safety
- Allow identification and early intervention of post-injection reactions
- Reduce the likelihood of re-exposure for patients who have had a previous hypersensitivity reaction to AVEED or its components

The REMS will consist of a Communication Plan, Medication Guide, and Assessments. The additional risk management interventions will consist of a controlled distribution system, educational materials, including a patient management algorithm, patient-wait-time adherence tools, and enhanced pharmacovigilance. The controlled distribution system will ensure that AVEED is only distributed to HCPs in order that it will be administered only in a healthcare setting. It will not be available to patients at retail pharmacies, which will reduce the chance of self-administration.

The goals of the REMS are to ensure that:

- HCPs and patients understand the risks of an injection-based POME reaction and an anaphylactic reaction following the administration of AVEED.
- Patients remain at the healthcare facility or doctor's office for 30 minutes to allow early recognition and management of an injection-based POME reaction or an anaphylactic reaction following the administration of AVEED.

### **1.6.1. The Communication Plan**

The Communication Plan consists of a Dear HCP Letter that is intended to inform prescribers about the risks of an injection-based POME reaction or an anaphylactic reaction following the administration of AVEED. A copy of the Package Insert and Medication Guide will be included with the Dear HCP Letter.

The content of the letter will include the importance of:

- Explaining the risks to patients
- Providing a Medication Guide to the patient with each injection

- The 30-minute in-office wait post-injection
- Not re-exposing patients who have had a previous hypersensitivity reaction to AVEED or its components
- Reporting adverse events (AEs) – especially an injection-based POME or an anaphylactic reaction – suspected to be associated with the administration of AVEED, and the various means of doing so

The additional risk management interventions include a patient management algorithm that will be distributed with the Dear HCP Letter. The patient management algorithm is designed to help with recognition and early intervention if a post-injection reaction occurs. Additional HCP and patient educational materials, including a video describing correct intramuscular (IM) injection technique (to reduce the likelihood of intravascular administration) and post-injection educational materials for patients, will be made available post-launch.

#### **1.6.1.1. Enhanced Pharmacovigilance Activities**

Endo will utilize a dual approach to monitoring and evaluating postmarketing AEs post-injection. For cases received spontaneously (traditional “passive” surveillance), Endo will utilize specialized collection forms to collect as much follow-up information as possible in a standardized fashion on all possible reports of injection-based POME reactions and anaphylactic reactions.

In addition, Endo will put into place an active surveillance program by partnering with groups that utilize electronic health record (EHRs). This will include EHRs utilized by urologists, who are likely to be early prescribers of AVEED, and EHRs more representative of primary care practices. By obtaining HIPAA-compliant data from these systems, Endo will be able to more accurately determine the rate of post-injection reactions in almost real-time in these patients because both the number of reactions and the number of injections administered will be known. Changes in the rate of reactions will direct subsequent actions to improve the safety of injections and potential modifications to the REMS.

### **1.7. Benefit-Risk Conclusion**

The Endocrine Society recommends testosterone replacement therapy for symptomatic men with classical androgen deficiency and in specific populations that may benefit from replacement therapy. Testosterone replacement can induce and maintain secondary sex characteristics, improve BMD, sexual function, sense of well-being, and muscle mass and strength.(3)

One of the key benefits of AVEED is continuous testosterone delivery over an extended period of time. The injection interval for AVEED, after the loading dose, is 10 weeks (≈5 injections/year) compared with daily treatment for the topical therapies or 2 to 4 week intervals (13 to 26 injections per year) for the IM testosterone enanthate replacement therapy. Reducing dosing frequency may improve patient persistence to medication. Persistence on therapy is important for achieving therapeutic benefit as well as evaluating response to therapy.

In clinical trials, AVEED demonstrated that 94.0 % of subjects maintained a  $C_{avg}$  testosterone concentration in the eugonadal range over the 10-week period dosing period. AVEED does not carry the risk of transference, which may harm children and women who are inadvertently

exposed to testosterone through contact with men taking commonly prescribed transdermal products. AVEED has extensive clinical and postmarketing safety data that support its safe use.

Safety data for AVEED are based on an extensive safety database of 18 completed clinical studies conducted in 3,556 subjects treated with TU. AE data from the US clinical study in hypogonadal men, European clinical studies in hypogonadal men, male contraception studies in healthy subjects, and postmarketing studies in hypogonadal men provide supportive evidence of the safety of AVEED. Furthermore, the safety profile is supported by the extensive (>3.1 million doses sold) and long-term (since 2003) marketing experience with Nebido (TU 1000 mg); in the 9 years since Nebido was first introduced, it has never been withdrawn from marketing for any reason (including for safety reasons) in any of the 94 countries in which it is approved.

The general safety profile is similar to other TRT products. Hypertension, prostatitis, increased prostate-specific antigen (PSA), acne, and sleep apnea syndrome are commonly reported with other TRTs and were observed in these trials.

Analysis of the TU exposure data from clinical and postmarketing studies in 3,556 subjects who received more than 20,000 injections indicates that immediate post-injection reactions are rare. The number of reported cases of immediate post-injection reactions has been low, and the reporting rate based on the postmarketing experience has remained low and constant over time.

The rate of POME cases from all clinical and postmarketing studies was 1.5 cases (95% CI, 0-3.2) of POME per 10,000 injections (Table 3), and the reporting rate of POME from the postmarketing experience data based upon clinical review is estimated to be 0.7 cases (95% CI, 0.6-0.8) of POME per 10,000 doses sold (Table 4).

No cases of anaphylaxis were identified by the investigators in the clinical trials. A retrospective review was performed using the Sampson criteria to define anaphylaxis. The rates of anaphylaxis from all clinical and postmarketing studies were 0 cases (95% CI, 0-10.4) per 10,000 patients (Table 3). The reporting rates of anaphylaxis cases from the postmarketing experience data based upon clinical review are estimated to be 0.4 cases (95% CI, 0.3-0.5) of anaphylaxis per 10,000 patients (Table 4).

**Table 3: Incidence Rates of Anaphylaxis and POME Based on Number of Injections, Patient-Years, and Patients in Clinical Studies**

	<b>Incidence Rate of Anaphylaxis (95% CI)</b>	<b>Incidence Rate of POME (95% CI)</b>
Number of Cases	0	3
Per 10,000 Injections (Total Number of Injection = 20,217)	0 (0, 1.8)	1.5 (0, 3.2)
Per 10,000 Patient-Years (Total Number of Patient-Years = 4221.9)	0 (0, 8.7)	7.1 (0, 15.1)
Per 10,000 Patients (Total Number of Patients = 3556)	0 (0, 10.4)	8.4 (0, 18.0)

**Table 4: Reporting Rates of Anaphylaxis and POME Based on Number of Doses Sold, Estimated Patient-Years, and Estimated Number of Patients from Postmarketing Surveillance**

	Reporting Rate of Anaphylaxis (95% CI)	Reporting Rate of POME (95% CI)
Number of Cases	45	223
Per 10,000 Doses Sold (Total Number of Dose Sold =3,107,652)	0.1 (0.1, 0.2)	0.7 (0.6, 0.8)
Per 10,000 Patient-Years (Estimated Total Number of Patient-Years = 722,709.8 <sup>a</sup> )	0.6 (0.4, 0.8)	3.1 (2.7, 3.5)
Per 10,000 Patients (Estimated Total Number of Patients = 1,213,654 <sup>b</sup> )	0.4 (0.3, 0.5)	1.8 (1.6, 2.1)

<sup>a</sup> Patient years were estimated from the 3,107,652 vials sold and an average dosing interval of 12 weeks, or 4.3 doses/year ( $52/12 \approx 4.3$ ) ( $722,709.8 = 3,107,652/4.3$ ).

<sup>b</sup> The total number patients treated with Nebido was 1,213,654, which was estimated as the quotient of the total patient years (722,709.8) and the estimated median time on therapy (0.595 year, N = 284).

In summary, the potential for POME and anaphylaxis exists for all oil based drug products administered IM. POME and anaphylaxis are well characterized clinical disorders that present in the post-injection period. In the clinical development program and in postmarketing surveillance experience, POME and anaphylaxis have been reported. There have been no reports of serious long-term sequelae, no deaths have been reported due to these reactions and lastly, the severity and nature of most of the events were such that they resolved spontaneously without requiring intervention. Because these events occur immediately post-injection, or shortly after, they can be identified and managed by HCPs with an appropriate risk management plan.

The short-acting testosterone injectable products also carry the risk of immediate post-injection reactions like cough and anaphylaxis. Based on a study by Mackey et al, 1.5% of injections (95% CI, 0.6%-2.9%) resulted in “cough events.”<sup>(1)</sup> Although post-injection cough is noted on the label of Delatestryl, a currently approved testosterone injectable product, the rate is not reported but it may be likely that rates are similar to TU. Because these products have been on the market for decades, spontaneous reporting rates of reactions are low but the occurrence of serious hypersensitivity reactions is also reflected in their labeling.

Although all AE is of concern, these particular immediate-post-injection reactions, POME and anaphylaxis, have certain characteristics which lend themselves to mitigation through HCP and patient education and additional safe use measures. Because of the proposed product distribution and administration plan, the patient will be in a healthcare setting during the immediate post-injection period, which allows for detection, monitoring, and, if necessary, management of the event.

Endo believes that AVEED has a favorable benefit risk profile for patients with low testosterone levels due to hypogonadism. AVEED with its unique benefits, offers another option for the patient and physician to consider. Endo is confident that the proposed REMS program, along with the product labeling and controlled distribution, will effectively mitigate the identified risks of AVEED, including POME and anaphylaxis.

## 2. INTRODUCTION

AVEED is a depot formulation of TU (750 mg TU) indicated for long-term testosterone replacement therapy in hypogonadal men. In adult males with conditions associated with a deficiency or absence of endogenous testosterone, IM administration of 750 mg AVEED maintains the average testosterone concentration within eugonadal range (300-1000 ng/dL) with low risk for exceeding  $C_{max}$  limits accepted by the FDA. Following baseline administration of 750 mg, a second 750 mg dose is given at 4 weeks followed by 750 mg every 10 weeks thereafter. AVEED (750 mg TU/3 mL) is the same drug formulation as Nebido (1000 mg TU/4 mL) which is approved in 94 countries (including the European Union and Australia). The treatment regimen approved worldwide is 1000 mg given at 10- to 14-week intervals with an optional dose given 6 weeks after the first dose. Between the launch of Nebido in 2003 and November 24, 2011, more than 3.1 million doses of Nebido have been sold worldwide providing extensive postmarketing safety experience.

The AVEED NDA was submitted on August 24, 2007. In 2009, the FDA issued a complete response letter stating that the AVEED formulation could not be approved due to FDA's concern regarding 2 types of immediate post-injection reactions. These reactions consisted of an acute coughing episode immediately after injection. The reaction is thought to be caused by oil from the injection entering the blood stream and reaching the lung. This event is known as pulmonary oil micro-embolism, or by the acronym "POME." FDA was also concerned about immediate post-injection reactions that included clinical features consistent with anaphylaxis.

After meeting with the FDA on 2 occasions to discuss approvability, including discussion of POME and anaphylaxis events that have been reported with other oil based products, Endo resubmitted the NDA on November 29, 2012 which presented additional data from a review of the clinical and postmarketing databases to identify and characterize all cases of POME and anaphylaxis. In addition to Endo's adjudication of potential POME and anaphylaxis cases an adjudication of potential POME and anaphylaxis cases by 2 independent adjudicators has been submitted to the FDA. These reviews were conducted to better assess the true rate of these post-injection reactions.

This briefing book provides a summary of the effectiveness and general safety experience with AVEED in clinical development and the safety experience reported in postmarketing with TU. Additional sections provide detailed findings from an independent adjudication of POME and anaphylaxis, a proposed Risk Evaluation and Mitigation Strategy (REMS), and finally, the overall benefit risk profile to support the approval of AVEED.

### **3. MEDICAL NEED IN MEN WITH ANDROGEN DEFICIENCY**

#### **3.1. Symptoms of Male Hypogonadism**

The Endocrine society defines hypogonadism in men as “a clinical syndrome that results from failure of the testis to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-testicular axis.”(3) Hypogonadism can be classified into primary or secondary testicular failure.(3)

Primary hypogonadism is related to a primary defect of the testes. Klinefelter’s syndrome is the most common congenital form of primary hypogonadism. Other causes of testicular failure can be due to cryptorchidism, bilateral testicular torsion, orchitis, orchidectomy, chemotherapy or toxic damage from alcohol or heavy metals. In the vast majority of cases, hypogonadism is related to a primary defect of the testes.

Secondary hypogonadism, which is less common, is caused by idiopathic gonadotropin releasing hormone (GnRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation.

Hypogonadism can also occur with dual defects that affect both the testis and the pituitary.

The clinical presentation of hypogonadism in men depends on the age of onset of androgen deficiency.(3) Prepubertal onset of hypogonadism presents with eunuchoidism, delayed development of secondary sex characteristics, and high pitched voice. In adult men (postpubertal), symptoms and signs are nonspecific and depend on many factors including age of onset and duration of the androgen deficiency.

Signs suggestive of androgen deficiency include loss of body (axillary and pubic) hair, reduced sexual desire, and reduced libido, breast discomfort, gynecomastia, shrinking testes, low trauma fracture, low BMD, hot flushes, and sweats.

Other, less specific signs and symptoms include decreased energy and motivation, depressed moods, poor concentration and memory, sleep disturbance, mild anemia, reduced muscle bulk and strength, increased body fat and BMI, and diminished physical or work performance.

The threshold testosterone level below the normal range at which symptoms of androgen deficiency and adverse health outcomes occur is not precisely defined. Based on the Endocrine Guidelines, for most symptoms, the average testosterone threshold corresponded to the lower limit of normal range for young men (~300 ng/dL).

#### **3.2. Benefit of Testosterone Replacement Therapy**

The Endocrine Society recommends replacement therapy for symptomatic men with classical androgen deficiency to induce and maintain secondary sex characteristics and to improve BMD, sexual function, sense of well-being, and muscle mass and strength.(3) The Endocrine Society recommends against a policy of offering testosterone therapy to all older men with low testosterone levels. Therapy should only be offered on an individual basis due to the uncertainty about the risk and benefits in this age group.

The guidelines also recommend evaluating patients 3 to 6 months after treatment initiation and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering any adverse effects, and to check compliance. The need to monitor long term therapy is based on the difference in target organ response to testosterone. Some effects of therapy are seen early for example, effects on sexual interest whereas; changes in body composition may not be observed for 3 months or greater.(4) The effect of testosterone replacement on BMD may become detectable after 6 month and continuing up to 2 to 3 years,(5) This is reflected in the guidelines which recommend monitoring for changes in BMD after 1 or 2 years on therapy.

### 3.3. Testosterone Replacement Therapies

Testosterone replacement therapies have been approved by the FDA since 1973. There are currently 5 routes of administration available including IM injection, transdermal (gels, solutions or patches), oral (not available in the United States), buccal adherent tablets, or pellets for implantation (Table 35). The therapeutic target is to increase serum testosterone levels into mid normal range for healthy young men. These formulations can deliver adequate TRT, although each has unique limitations and risks. More than 95% of hypogonadal men choose either a transdermal or IM injectable route. Most patients (≈65%) choose transdermal gel or solution formulations. Although these products, which include the 3 most recently approved TRTs, AndroGel® 1.62%, Axiron®, and FORTESTA®, achieve acceptable levels of testosterone replacement (≈77% to 87% of men maintain average daily testosterone concentrations within the eugonadal range), they require daily application, require adequate product drying time (2½ to 5 minutes) prior to getting dressed and can cause skin reactions. Most, importantly, all have the potential for causing secondary exposure to women or children. The secondary exposure, or transference, can cause virilization in women and children and irreversible changes in children (eg, fusion of bone plates), which led the FDA to require Black Box warnings about transference on all of these products. The Pediatric Advisory Committee Meeting on June 23, 2009 held an expanded review of AEs and overview of secondary exposure of testosterone in children (labeling – black box warning/medication guide). The committee recommended measures to be taken immediately to reduce risk of exposure including changing skin application sites and limiting use in families with children. The Committee also provided specific labeling recommendations including (1) revising text using descriptive, easy to understand language, (2) defining the term “virilization” for the consumer (3) adding information on the pediatric studies performed and the risks other than just bone effects, of secondary exposure to Section 8.4 Pediatric Use, and (4) revising the illustration to be consistent with application instructions.

Depot testosterone formulations which are dosed IM include testosterone enanthate and testosterone cypionate. About 30% of men treated for hypogonadism use these formulations. These products are formulated in an oil-based vehicle and are administered every 2 to 4 weeks, therefore requiring 13 to 26 doses per year. They do not have the risk of transference, but like AVEED, are in an oil-based vehicle, so they also carry the risk of immediate post-injection reactions like cough, respiratory distress and anaphylaxis. These short-acting injectable products have the potential to cause supraphysiological levels of testosterone.

The less commonly used formulations also have limitations. Oral testosterone replacement therapy utilizes 17α-methyl-testosterone which can cause liver injury. Buccal formulations are associated with gum-related AEs, and pellets require surgical implantation.

### **3.4. Testosterone Undecanoate Has Benefits That Can Provide Another Option for Patients**

#### **3.4.1. Extended Dosing Interval**

One of the key benefits of AVEED is continuous testosterone delivery over an extended period of time. The injection interval for AVEED, after the loading dose, is 10 weeks ( $\approx 5$  injections per year) compared with daily treatment for the topical therapies or 2 to 4 week intervals (13 to 26 injections per year) for the IM testosterone enanthate replacement therapy. Reducing dosing frequency may improve patient persistence to medication. In other therapeutic areas, it has been shown that less frequently dosed products like Boniva® (once monthly) have better patient persistence than product dosed daily and weekly.

#### **3.4.2. Efficacious**

AVEED is efficacious with 94.0% of subjects achieving normal testosterone blood levels, defined as within  $C_{avg}$  300 to 1000 ng/dL, and only 5.1% of subjects with levels below the therapeutic range ( $C_{avg} < 300$  ng/dL). Other recently approved products also used the same criteria for approval. The percentage for topical formulations ranges from 77% to 87%. Other TRT products (short acting parenteral testosterone products and testosterone topical formulations) may require dose adjustment to achieve adequate serum testosterone levels.

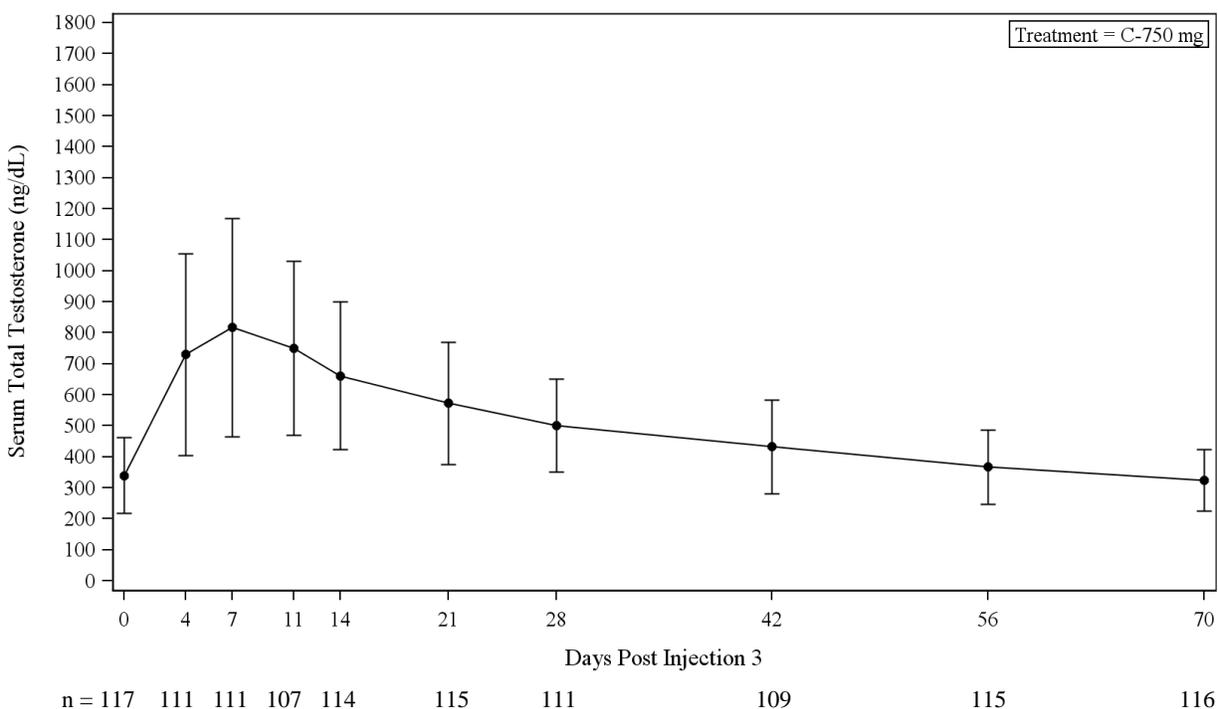
#### **3.4.3. No Risk of Transference**

Unlike the transdermal gel formulations which are the most widely used products in the United States, there is no potential for unintended transfer of testosterone to women or children from men receiving AVEED. Even small quantities of testosterone, transferred on a repeated basis to these individuals, may result in the clinical signs and symptoms of hyperandrogenism. In women, this can manifest as virilization and in children this can manifest as enlargement of the penis or clitoris, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. In most cases, these signs and symptoms regressed with removal of the exposure to testosterone gel. In a few cases, however, enlarged genitalia did not fully return to age-appropriate normal size, and bone age remained modestly greater than chronological age. These safety concerns have resulted in the inclusion of a black box warning regarding secondary exposure on the package inserts of topical TRTs. These products also require a Medication Guide as part of the REMS. Despite the change in labeling, the black box warning, and the REMS, there continue to be reports of AEs due to transference.

#### **3.4.4. Mean Testosterone Levels Do Not Exceed Supraphysiological Testosterone Levels**

In the Phase 3 pivotal study (IP157-001 Part C and C2), treatment with AVEED 750 mg maintained mean testosterone concentrations in the eugonadal range over 10 week dosing interval (Figure 3). In contrast, for short acting injectable products, serum testosterone levels rise into the supraphysiological range, then decline gradually by the end of the dosing cycle (Figure 4).

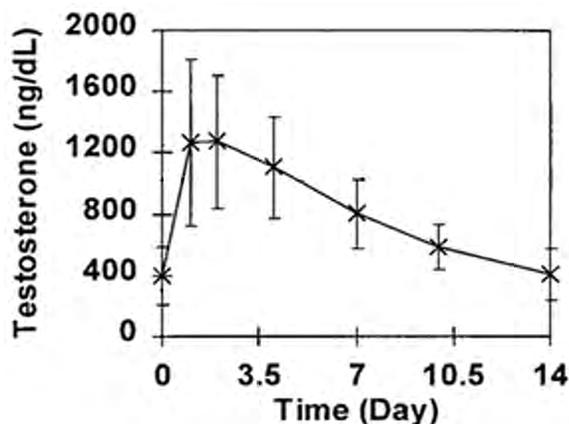
**Figure 3: Mean (SD) Serum Total Testosterone Concentrations (ng/dL) Resulting from the 3<sup>rd</sup> Intramuscular Injection of Testosterone Undecanoate**



Data Source: 5.3.5.1, Study IP157-001 Part C&D [Figure 14.2.1]

Note: C-750 mg refers to TU 750 mg.

**Figure 4: Steady-State Pharmacokinetic Profiles of Testosterone from Biweekly Intramuscular Injections of Testosterone Enanthate Measured at Week 16**



Data Source: *J Clin Endocrinol Metab.* 1999;84:3472.(6)

### 3.4.5. Persistence of Testosterone Replacement Therapy

Persistence on therapy is important for confirming the diagnosis of hypogonadism and achieving therapeutic benefit. The Endocrine Society guidelines recommend a therapeutic trial of adequate duration (3 to 6 months) to assess response to therapy. One of the challenges of testosterone

replacement with currently available products in the United States is that persistence is poor. Prescription data from the United States show that over 60% of hypogonadal men discontinue TRTs within 6 months. Only 41% of men remain on transdermal gel products and only 29% of men remain on short acting injections at 6 months (Truven Health Analytics MarketScan® database). Because of this lack of persistence with treatment in many men, it will remain unclear whether the diagnosis is accurate and in those who are hypogonadal, the benefits will not be maintained.

To understand whether the availability of a long-acting depot injectable (eg, TU) impacts medication persistence (the duration of time from initiation to discontinuation of therapy), we analyzed prescription claims data (IMS Longitudinal Prescription:LRx) from Germany where TU injection (marketed under the trade name of Nebido) has been available as a treatment option since 2004. Germany has the largest TRT volume in Europe. These data contains approximately 64,000 TRT prescriptions from January 2008 to August 2012. The data, which represent approximately 80% of the German population, are regarded as a reliable prescription claims source and are commonly used by healthcare organizations and regulatory agencies.

The data show (Table 5) that 26.1% of patients remained on transdermal gel products and 4.9% remained on the short-acting injectable products at 6 months. In contrast, TU injection had a longer duration of persistence. Patient persistence was 56.2% at 6 months which is approximately 2-fold higher than attained with the transdermal gels. This indicates that an adequate therapeutic trial of TRT can be achieved in more men on TU injection than on the other formulations.

**Table 5: Persistence of Testosterone Replacement Therapy Products Up to 2 Years – German IMS®LRx Database**

Formulation (Total Patients)	Persistence (%) in Germany IMS®LRx Database			
	90 days (3 months)	180 days (6 months)	360 days (1 year)	720 days (2 years)
Any Testosterone Therapy (n=17,385)	45.2	32.7	18.6	10.3
Transdermal Gels (n=7,609) <sup>a</sup>	39.1	26.1	12.4	5.7
Short-Acting Injections (n=4,702) <sup>b</sup>	14.7	4.9	1.6	0.5
TU Injection (testosterone undecanoate) (n=4,663)	70.1	56.2	34.7	20.2

<sup>a</sup> Transdermal Gels: Androtop gel, Testim, Tostran, Testotop

<sup>b</sup> Short-Acting Injections: Testosterone Depot, Testosterone Enanthate, Testoviron

Also shown are the observed 1-year and 2-year persistence rates of these products (Table 5). Again, persistence remained higher for TU injection than for other formulations suggesting that a greater proportion of men needing therapy will remain on therapy with TU injection.

As observed from the German data, patient persistence declines over time, similar to what was observed in the US MarketScan data. Although we cannot know what impact the availability of a long-acting injection option might have on treatment of men in the United States, it is not

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unreasonable to think that AVEED may demonstrate a pattern of persistence in the United States similar to that seen in Germany.

The AVEED injection interval of every 10 weeks may be contributing to the persistence observed. AVEED will have also have the advantage of administration within a healthcare setting, thus confirming that the patient will be compliant. This is unlike topical gels and short-acting injectables which are dosed daily and weekly, respectively, and can be administered by the patient at home. Because patients do not always take their TRTs as directed, confirmation of the diagnosis may be lacking and, clinical benefit may not always be attained in those who need it.

## **4. OVERVIEW OF AVEED CLINICAL DEVELOPMENT PROGRAM**

### **4.1. Summary**

- AVEED is an established formulation of TU administered as 750 mg at initiation, 750 mg at week 4 and then 750 mg every 10 weeks thereafter.
- Nebido is the same formulation as AVEED approved in 94 countries and administered at 1000 mg at initiation, at week 6 and then as a dose of 1000 mg every 10 to 14 weeks. There is significant postmarketing experience with Nebido.
- FDA did not approve AVEED because of concerns about immediate post-injection reactions
- The TU development program followed 3,556 subjects treated with 750 and 1000 mg including 2424 subjects who were followed in Nebido postmarketing studies. Endo resubmitted the AVEED NDA to provide additional analyses of the incidence and severity of POME and anaphylaxis in clinical development and in the spontaneous postmarketing experience with Nebido.

### **4.2. Overview of AVEED**

The AVEED formulation contains 750 mg TU in a castor oil vehicle and benzyl benzoate to extend release of testosterone. Benzyl benzoate also increases injectability.

AVEED is the same formulation as Nebido (1000 mg TU), which is manufactured and marketed worldwide by Bayer AG, Germany. The first marketing authorization for Nebido was granted in Finland on November 25, 2003. Nebido is currently approved in 94 countries. The treatment regimen approved worldwide is 1000 mg (4 mL dose) at 10- to 14-week intervals with an optional loading interval of a minimum of 6 weeks between the first 2 injections. Through November 24, 2011, the worldwide sales of Nebido amounted to more than 3.1 million doses, corresponding to 722,709 treatment years.

Following IM injection of TU in a castor oil vehicle, TU is gradually released from the depot. TU is cleaved by serum esterases into testosterone and undecanoic acid. An increase in serum levels of testosterone above basal values may be seen as early as 1 day after administration. Following IM administration, the plasma concentration versus time profile reflects the slow release rate from the depot. Sustained concentrations above baseline values are observed for up to 10 weeks, compared to 2 to 4 weeks for other testosterone products administered via the IM route.

### **4.3. Regulatory History**

NDA 22-219 was originally filed by Indevus on August 24, 2007. An “approvable” letter with clinical deficiencies was received on June 27, 2008 and a resubmission was then made on March 2, 2009. Endo acquired AVEED from Indevus on March 23, 2009.

On December 2, 2009, Endo received a Complete Response from the FDA. The response outlined the reasons for the FDA determination that the NDA could not be approved in its present form. The FDA stated the following:

“Based on the reports of these serious, immediate and potentially life-threatening post-injection adverse reactions, we do not believe that the demonstrated benefits of the drug outweigh the additional potential risks associated with the use of TU.

Although the exact etiology of these adverse reactions has yet to be determined, some of the reactions included clinical features consistent with anaphylaxis or angioedema and POME.”

In the complete response letter the FDA suggested 2 approaches to address the issue.

1. Subsequently reformulate the product and show that the reactions have been reduced or mitigated, or
2. Identify a population of adult males who require testosterone replacement therapy and in whom the additional potential risks associated with the use of TU as currently formulated would be acceptable

AVEED has 3 components: TU (active ingredient), castor oil (solvent), and benzyl benzoate (co-solvent). As part of the AVEED manufacturing process, TU is dissolved completely in benzyl benzoate and castor oil is added to dilute to the final concentration (250 mg/mL). The product is sterile filtered and aseptically filled.

Both castor oil and benzyl benzoate are listed in the US FDA Inactive Ingredient database and are used in other drug products. Both excipients are tested to ensure they meet the compendial requirements included in the United States Pharmacopoeia and National Formulary (USP-NF) and European Pharmacopoeia (Ph. Eur.) monographs. Approved IM injection products containing oils/benzyl benzoate are listed in [Table 6](#) with absolute amounts injected based on dosing regimen presented in [Table 7](#).

Testosterone esters and other hormones are typically formulated as oily solutions for IM injection to ensure the prolonged duration of action. The combination of castor oil and benzyl benzoate provides the prolonged release characteristics of the depot and the appropriate viscosity for injectability. The current AVEED formulation was selected after extensive testing to achieve the desired pharmacokinetic characteristics which in addition to restoring patients' testosterone to the eugonadal range also results in an extended dosing interval. Thus, all components in the formulation are necessary to achieve the desired drug and release characteristics.

The absorption of drugs in injectable (parenteral) oil solutions may vary substantially with the composition of the vehicle including the type of oil employed. Reformulation of AVEED in a different oil solution would create a new drug product that would not have the benefit of the extensive post-marketing safety experience that AVEED shares with NEBIDO.

Endo also evaluated the medical literature to determine if it was possible to identify a subpopulation of hypogonadal males for treatment with AVEED, with a more favorable benefit-risk profile. After reviewing the available data, it was determined that specific risk factors to identify men at higher risk for acute post-injection reactions could not be identified. Therefore, in discussions with the FDA, a plan for enhanced risk management activities was put

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forward which could address the main elements of risk for all hypogonadal men. The REMS is discussed later in this document (section 8).

After meeting with the FDA on 2 occasions to discuss approvability, including discussion of POME and anaphylaxis events that have been reported with other oil based products, FDA suggested that Endo resubmit the NDA. The FDA suggested that the issue would most likely go to an advisory committee for discussion.

A resubmission of the NDA on November 29, 2012 included additional findings from an Endo search of the TU clinical and TU postmarketing databases to identify and characterize all cases of POME and anaphylaxis. In addition, recently completed adjudication of potential POME and anaphylaxis cases by 2 independent adjudicators has been submitted to the FDA. The resubmission also included a proposed risk management plan that includes a Medication Guide requiring a 30-minute waiting period after each injection. Endo believes the medically serious AEs that occur immediately after injection are rare, detectable and manageable, characteristics which support a favorable benefit risk profile, in conjunction with the proposed REMS.

**Table 6: Approved Intramuscular Injection Products Containing Benzyl Benzoate and/or Castor Oil**

Product	Indication	Dosage	Benzyl Benzoate Content	Castor Oil Content
BAL in Oil (dimercaprol)	Treatment of arsenic, gold and mercury poisoning	3 mL ampule	200 mg (20% w/v)	700 mg (70% w/v) (peanut oil)
Depo-Testosterone (testosterone cypionate)	Primary hypogonadism (congenital or acquired)- Hypogonadotropic hypogonadism (congenital or acquired)	10 mL vial (100 mg/mL) 1 and 10 mL vials (200 mg/mL) Replacement in the hypogonadal male, 50 to 400 mg administered every 2-4 weeks	224 mg (22% w/v)	560 mg (56% w/v, cottonseed oil)
Estradiol Valerate Injection 20 and 40 mg/mL [Sandoz Inc]	Treatment of moderate to severe vasomotor symptoms associated with the menopause; Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered; Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure; Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only).	5 mL multi-dose vials (20 & 40 mg/mL) Severe vasomotor symptoms and hypoestrogenism, 10-20 mg every 4 weeks Advanced androgen-dependent carcinoma, 30 mg every 1-2 weeks	20-224 mg (22% w/v) 40-447 mg (45% w/v)	20-736 mg (74% w/v) 40-493 mg (49% w/v)
Faslodex (fulvestrant)	Treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy	5 mL syringe (50 mg/mL) 250 mg & 500 mg every 2 weeks for 1 month (monthly thereafter)	168 mg (15% w/v)	650 mg (65% w/v)
Makena (hydroxyprogesterone caproate)	Reduce risk of pre-term birth in women with singleton pregnancy who have a history of singleton spontaneous preterm birth	5 mL multidose vial (250 mg/mL) Weekly dose – 350 mg (1 mL)	515 (46% v/v)	285 (28.6% v/v)
Delatestryl		200 mg/mL TE 50-400 mg every 2-4 weeks	None	795 mg (sesame oil)
AVEED	Testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests	3 mL vial 750 mg every 10-14 weeks	500 mg (47.8% w/w)	295 mg (28.2% w/w)

**Table 7: Absolute Amounts of Benzyl Benzoate and Oils Per Dosing Regimen**

Product	Dosing Regimen	Benzyl Benzoate (mg)	Castor Oil (mg)	Dosing Period
BAL Oil		6000	2100 (peanut oil)	10-13 days (2 weeks)
Depo-Testosterone (testosterone cypionate)	2 mL every 2 weeks	448	1120 (cottonseed oil)	2 weeks
Estradiol Valerate Injection 20 and 40 mg/mL [Sandoz Inc]	20 mg every 4 weeks	224	736	4 weeks
Faslodex (fulvestrant)	500 mg 3 times in month 1	1680	6500	4 weeks
Makena (hydroxyprogesterone caproate)	350 mg per week	515	285	1 week
Delatestryl	400 mg every 2 weeks		1590 (sesame oil)	2 weeks
AVEED	750 mg every 10-14 weeks	1500	885	10 weeks

#### 4.4. Overview of Clinical Studies

Evidence supporting the restoration and maintenance of testosterone at eugonadal levels (300-1000 ng/dL) is provided in the open-label, single-arm US study IP157-001, and safety of TU is derived from 18 clinical studies conducted in 3,556 subjects treated with 750 mg and/or 1000 mg TU (Table 36). One (1) study was conducted in the United States, 16 studies were conducted in Europe, and 1 study was international enrolling subjects from Europe and Korea.

Of the 18 studies, 13 were conducted in males with hypogonadism with 6 of these conducted as postmarketing studies with TU. Five (5) contraception studies were conducted in healthy males. Currently, there is 1 ongoing study (IP157-003) which is a re-challenge study for subjects who have had a possible anaphylaxis event. To date, 1 subject has been enrolled in study IP157-003.

The goal in replacement of most endogenous hormones (eg, thyroid, testosterone) is normalization to a level that eliminates the signs and symptoms of deficiency. Development of products for testosterone replacement focuses on maintaining eugonadal testosterone concentration (300-1000 ng/dL) without producing significant risk for exceeding  $C_{max}$  limits accepted by FDA on recently approved products. FDA approval of recently marketed TRTs was based upon the following criteria:

- $\geq 75\%$  patients have testosterone  $C_{avg}$  within the eugonadal range (300-1000 ng/dL), and the lower limit of the 95% CI for percent of subjects with  $C_{avg}$  within the eugonadal range is  $\geq 65\%$ .
- $\geq 85\%$  patients have  $C_{max} \leq 1500$  ng/dL.

- ≤5% of patients have  $C_{max}$  between 1800 and 2500 ng/dL
- No patients whose  $C_{max} > 2500$  ng/dL

Study IP157-001 was conducted in the United States to demonstrate the effectiveness of TU in restoring testosterone levels to eugonadal levels in hypogonadal men. This study enrolled hypogonadal men from the United States and was designed in 5 parts under one protocol (Parts A, B, C, C2, and D). Parts A, B, C, and C2 enrolled separate cohorts while Part D, evaluating subcutaneous administration, drew patients from Parts A and C in a crossover design. Parts A and B evaluated testosterone pharmacokinetics at different doses (1000 mg and 750 mg) and administration schedules following IM administration in order to select an optimal dosing regimen for further evaluation in Parts C and C2. Parts C and C2 were considered pivotal in establishing the effectiveness of TU utilizing the recommended dose strength and regimen (750 mg IM at baseline, at 4 weeks and then every 10 weeks thereafter). Part D evaluated subcutaneous dosing of 750 mg TU but this route of administration was not pursued further. Further details are presented in Table 8. It should be noted that the dose used throughout the world is 1000 mg (4 mL) while the dose proposed in the United States is 750 mg (3 mL). When this 1000 mg dose was tested in study IP157-001,  $C_{max}$  exceeded criteria set by FDA. Therefore, the dose was decreased to 750 mg which gave acceptable  $C_{max}$  levels.

Part C focused on the evaluation of  $C_{avg}$  and  $C_{max}$  data collected following the 3rd and 4th injection, while Part C2 examined the  $C_{max}$  after the 2nd injection. The rationale for evaluating  $C_{max}$  after the second injection was that this injection was administered 4 weeks after the first dose, while subsequent doses were administered 10 weeks apart. The pharmacokinetic results following the 3rd injection were defined as the primary analysis. The pharmacokinetic results following the 2nd and 4th injection were supportive. Both parts provided significant safety data, with subjects in Part C receiving up to 9 injections (84 weeks) while in Part C2 subjects could receive up to 6 injections (64 weeks). The study design, methodology and findings of the pivotal parts of study IP157-001 (Parts C and C2) are presented in the following section.

**Table 8: Study IP157-001**

Study Part	Number of Patients	Single Dose	Dose Interval	Median Duration (weeks)
Part A (Dose and administration evaluation)	237	750 mg or 1000 mg IM	Q12 weeks	153.4
Part B (Dose and administration evaluation)	134	750 mg or 1000 mg IM	8 week (loading), Q12 weeks	90.1
Part C (Pivotal)	130	750 mg IM	4 week (loading), Q10 weeks	84.0
Part C2 (Pivotal)	23	750 mg IM	4 week (loading), Q10 weeks	54.1
Part D (Exploratory)	43 (Patients from Part A and Part C)	750 mg or 1000 mg SC	Q12 weeks	

## 5. PHARMACOKINETIC EFFECTIVENESS IN STUDY IP157-001: PARTS C AND C2

Treatment with IM TU dosed at 750 mg at baseline, 4 weeks, and then every 10 weeks thereafter maintained average testosterone levels in the eugonadal range (300 to 1000 ng/dL). The findings for the primary analysis based on  $C_{avg}$  and  $C_{max}$  levels during the 3rd injection, met all prespecified criteria. The findings were as follows:

After the 3rd injection

- 94.0% of subjects had  $C_{avg}$  in the eugonadal range (95% CI, 89.7-98.3).
- 92.3% of subjects had  $C_{max} \leq 1500$  ng/dL,
- 0% of subjects had  $C_{max} \geq 1800$  to  $\leq 2500$  ng/dL.
- No subjects had  $C_{max} > 2500$  ng/dL.

The supportive analyses also met the prespecified criteria. The findings were as follows:

After the 2nd injection

- 95.7% of subjects had  $C_{max} \leq 1500$  ng/dL and no subjects had  $C_{max} \geq 1800$  to  $\leq 2500$  ng/dL or  $> 2500$  ng/dL.

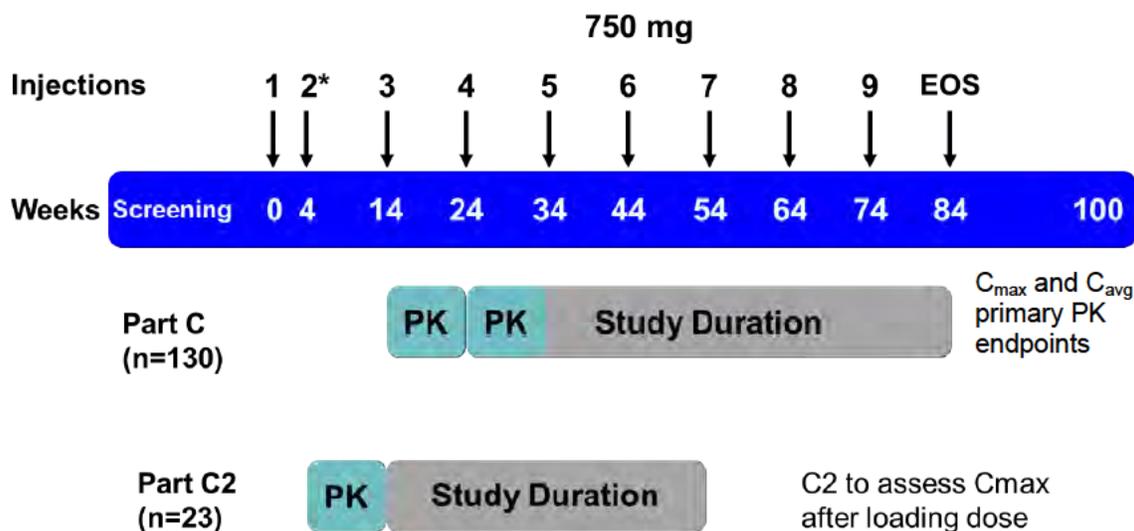
After the 4th injection

- 96.2% of subjects had  $C_{avg}$  in the eugonadal range (95% CI, 92.5-99.8).
- 92.0% of subjects had  $C_{max} \leq 1500$  ng/dL,
- 3.8% of subjects had  $C_{max} \geq 1800$  to  $\leq 2500$  ng/dL.
- No subjects had  $C_{max} > 2500$  ng/dL.

### 5.1. Study Design

The pivotal parts of study IP157-001 were Part C and C2 in which 750 mg of TU was administered at the first study visit followed by 750 mg at week 4 and then 750 mg every 10 weeks thereafter. Subjects included in Part C were naïve to IM TU. Part C consisted of a screening phase of 5 weeks during which subjects were washed out from prior TRT. Following baseline data collection, subjects entered Part C of the study. Intensive pharmacokinetic sampling, following the 3rd and 4th injections, was collected over the 10 week period. Trough levels were also collected prior to each of the first 8 injections. In Part C2 of study IP157-001, TU was administered at 750 mg using the same schedule as in Part C. However, intensive pharmacokinetic samples were collected around the time of  $C_{max}$  following injection 2. This injection was administered 4 weeks after the initial dose, during which the maximal concentration was expected.

Overall, 130 patients were enrolled into Part C with each subject treated for up to 9 injections over 84 weeks. In Part C2, 23 subjects were treated with up to 6 injections over 64 weeks.

**Figure 5: Study Design for Part C and C2 in Study IP157-001**


\*Loading Dose

### 5.1.1. Study Population and Pharmacokinetic Analysis

Pharmacokinetic criteria achieved by recently approved testosterone replacement products, are provided in section 4.4. The same criteria were used to assess C<sub>avg</sub> and C<sub>max</sub> after the 3rd and 4th injection in Part C and C<sub>max</sub> after the 2nd injection in Part C2.

Analytic study populations were defined as follows.

- Total Patient Sample is defined as those patients who were enrolled and given at least 1 injection.
- PK Population is defined as (Part C) patients with  $\geq 4$  total testosterone concentration values during the 3rd injection interval, or (Part C2) patients who received injection 2 and had at least 1 pharmacokinetic sample collected after injection 2. In both parts, data from patients with use of TRT outside of the protocol and those weighing <65 kg were excluded. The <65 kg weight exclusion was based on negotiations with the FDA on how the product is intended to be labeled. Low body weight may predispose patients to testosterone peak concentration in excess of the 2500 ng/dL threshold.

Pharmacokinetic parameters were calculated from the serum concentration data using non-compartmental methods within each patient. Nominal (protocol-scheduled) time from dosing was used to estimate all individual (within-patient) pharmacokinetic parameters. Parameters were derived for the 3rd and 4th injection intervals of Part C and the 2nd injection interval of Part C2, where intensive pharmacokinetic samples were collected. WinNonLin® Professional version 5.3 (Pharsight Corp., Mountain View, California) was used to derive pharmacokinetic parameters.

For the primary analyses, the proportion of patients whose C<sub>avg</sub> were within 300 and 1000 ng/dL and its 2-sided 95% CI were calculated. The 95% CI was calculated using normal approximation

method; the proportions of patients whose  $C_{max}$  were in the range of <1500 ng/dL, between 1800 and 2500 ng/dL, and >2500 ng/dL were calculated.

## 5.2. Pharmacokinetic Results from Part C

### 5.2.1. Subject Disposition

Part C enrolled 130 subjects with 71.5% completing the 84-week treatment phase (Table 9). Of the 130 subjects, 117 were included in the PK population for primary analysis. For Part C2, all 23 subjects were included in the PK population. Thirty seven (37) subjects withdrew from Part C, 15 had an AE associated with discontinuation and 10 withdrew consent. Two (2) subjects discontinued from Part C2, 1 discontinued because of an AE and 1 withdrew consent.

**Table 9: Patient Disposition, Pharmacokinetic Population**

	<b>Part C 750 mg (N=130)</b>	<b>Part C2 750 mg (N=23)</b>
Total Patient Sample	130 (100.0%)	23 (100.0%)
PK Population	117 (90.0%)	23 (100.0%)
Patients Completed Treatment Phase		
Yes	93 (71.5%)	21 (91.3%)
No	37 (28.5%)	2 (8.7%)
Reason for Discontinuation		
Adverse Event	15 (11.5%)	1 (4.3%)
Protocol Violation	0	0
Patient Withdrew Consent	10 (7.7%)	1 (4.3%)
Patient Non-Compliance	5 (3.8%)	0
Lost to Follow-up	3 (2.3%)	0
Other	4 (3.1%)	0

Data Source: 5.3.5.1, Study IP157-001 Part C&D [Table 14.1.2] and Study IP157-001 Part C2 [Table 14.1.2]

### 5.2.2. Baseline Characteristics

All patients were hypogonadal men. In Part C, the mean age of patients was 54.2 years (range: 24 to 75 years) and the majority of patients (74.6%) were white. The mean serum total testosterone concentration at screening in the Part C population was 214.7 ng/dL (range, 24.0 to 299.0 ng/dL). Use of at least 1 prior testosterone medication was reported by 62.3% of patients in Part C. Baseline characteristics of Part C2 were similar to those of Part C (Table 10).

**Table 10: Patient Demographic Characteristics, Total Patient Sample**

	<b>C-750 mg (N=130)</b>	<b>C2-750 mg (N=23)</b>
Age (years)	n=130	n=23
Mean ± Std. Dev.	54.2 ± 10.25	53.3 ± 10.35
Median	55.0	54.0
Minimum, Maximum	24, 75	30, 71
Race, n (%)	n=130	n=23
White	97 (74.6%)	18 (78.3%)
Asian	0	0
Black	16 (12.3%)	4 (17.4%)
Hispanic	14 (10.8%)	1 (4.3%)
Other	3 (2.3%)	0
Baseline Weight (kg)	n=129	n=23
Mean ± Std. Dev.	101.2 ± 17.96	107.3 ± 21.24
Median	100.8	105.3
Minimum, Maximum	59, 158	72, 152
Baseline Height (cm)	n=130	n=23
Mean ± Std. Dev.	177.9 ± 7.57	178.7 ± 8.85
Median	177.80	177.8
Minimum, Maximum	152, 193	160, 196
Body Mass Index (BMI) (kg/m <sup>2</sup> )	n=129	n=23
Mean ± Std. Dev.	32.0 ± 5.40	33.6 ± 6.31
Median	31.30	34.3
Minimum, Maximum	17, 51	23, 48
Inclusion Screening Total Testosterone (ng/dL)	n=130	n=22
Mean ± Std. Dev.	214.7 ± 68.57	197.6 ± 75.81
Median	236.1	220.6
Minimum, Maximum	24, 299	29, 279

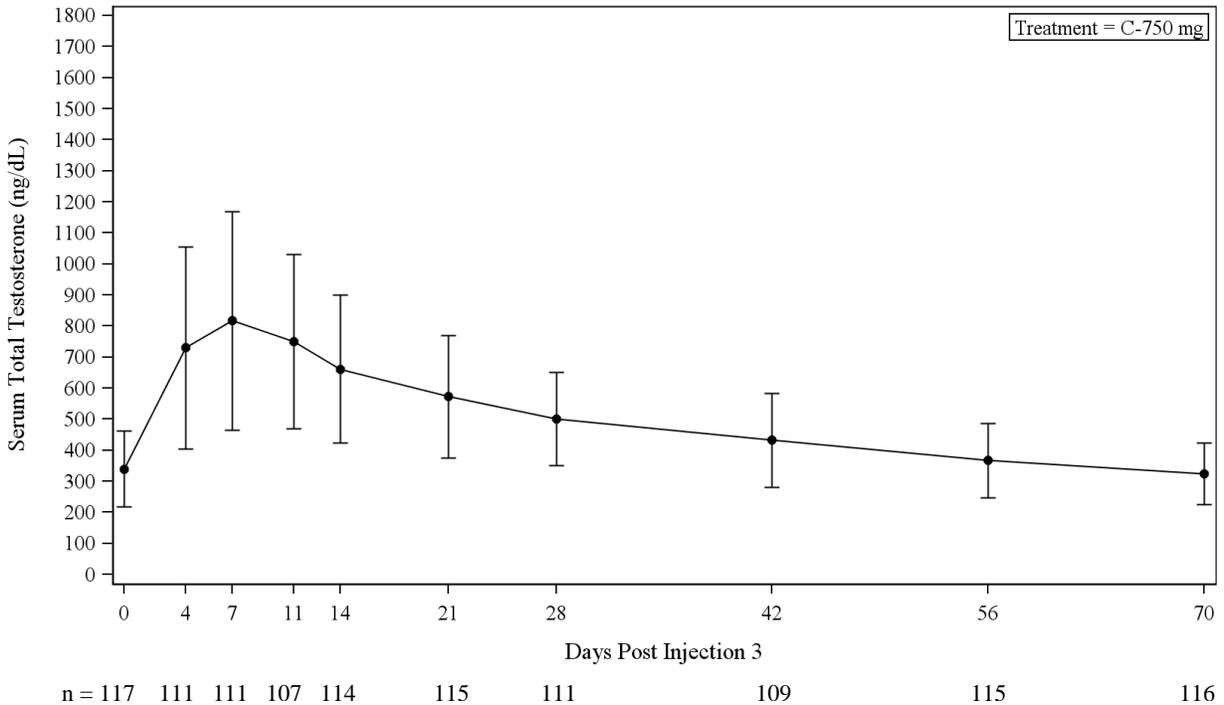
Data Source: 5.3.5.1, Study IP157-001 Part C&D [Table 14.1.3] and Study IP157-001 Part C2 [Table 14.1.3]

### 5.2.3. Pharmacokinetic Results

#### 5.2.3.1. Pharmacokinetic Results for the 3rd Injection

The mean serum total testosterone concentration over time after the 3rd injection is shown in (Figure 6). Mean serum testosterone levels reached their peak value on day 7. Mean value at day 70 (trough value before the 4th injection) was 323.5 ng/dL.

**Figure 6: Mean (SD) Serum Total Testosterone Concentrations (ng/dL) Resulting from the 3<sup>rd</sup> Intramuscular Injection of Testosterone Undecanoate, Pharmacokinetic Population**



Data Source: 5.3.5.1, Study IP157-001 Part C&D [Figure 14.2.1]

Note: C-750 mg refers to TU 750 mg.

The pharmacokinetic results following the 3<sup>rd</sup> injection were defined as the primary analysis (Table 11). Overall 94.0% of subjects (110 of 117) had  $C_{avg}$  between 300 and 1000 ng/dL with a lower limit of the 95% CI of 89.7%. More than 85% of subjects had  $C_{max}$  no greater than 1500 ng/dL and no subjects had values greater than 1800 ng/dL. All predefined success criteria were met.

**Table 11: Findings in Study IP157-001 During the 3rd Injection Interval and Listed Criteria for Success**

PK Parameter	Range (ng/dL)	Success Criterion	Findings TU 750 mg (N=117)
C <sub>avg</sub> (ng/dL)	300 - 1000	≥75% of subjects	110 (94.0%)
		The lower limit of the 95% CI of the percent of subjects meet the criterion ≥65%	(89.7%, 98.3%)
C <sub>max</sub> (ng/dL)	≤1500	≥85% subjects	108 (92.3%)
	>1500 to <1800		9 (7.7%)
	Between 1800 and 2500	≤5% subjects	0
	>2500	0 subjects	0

The summary of duration of serum total testosterone concentration above 300 ng/dL is given in Table 12. The mean serum total testosterone concentration over the 10-week dosing interval was within the eugonadal range (300–1000 ng/dL). The median duration of serum total testosterone concentration above 300 ng/dL was 70 days, which is the length of proposed dosing interval.

**Table 12: Summary of the Duration of Serum Total Testosterone Concentration During the 3rd Dosing Interval, Pharmacokinetic Population**

N	117
Median (95% CI)	70 (69, NC)

NC=Non-calculable

### 5.2.3.2. Pharmacokinetic Findings During 2nd Injection in Part C2

The C<sub>max</sub> measured during the 2nd injection interval meet pre-specified criteria (Table 13). Administration of TU given IM, 4 weeks after the 1st dose did not exceed C<sub>max</sub> concentration limits.

**Table 13: Number (%) of Patients Meeting Serum Total Testosterone C<sub>max</sub> Criteria for Success During the 2nd Injection Interval**

PK Parameter	Range (ng/dL)	Success Criterion	Findings TU 750 mg N = 23
C <sub>max</sub> (ng/dL)	≤1500	≥85% subjects	22 (95.7%)
	>1500 to <1800		1 (4.3%)
	Between 1800 and 2500	≤5% subjects	0
	>2500	0 subjects	0

### 5.2.3.3. Pharmacokinetic Findings for the 4th Injection

The pre-specified criteria during the 4th injection interval were identical to the primary analysis conducted during the 3rd injection interval. Results were comparable to those during the 3rd injection (Table 14).

**Table 14: Number (%) of Patients Meeting Serum Total Testosterone  $C_{avg}$  and  $C_{max}$  Criteria for Success During the 4th Injection Interval**

PK Parameter	Range (ng/dL)	Success Criterion	Findings TU 750 mg N = 104
$C_{avg}$ (ng/dL)	300 – 1000	≥75% of subjects	100 (96.2%)
		The lower limit of the 95% CI of the percent of subjects meet the criterion ≥65%	(92.5%, 99.8%)
$C_{max}$ (ng/dL)	≤1500	≥85% subjects	96 (92%)
	>1500 to <1800		4 (3.8%)
	Between 1800 and 2500	≤5% subjects	4 (3.8%)
	>2500	0 subjects	0

### 5.2.3.4. Trough Concentrations During Study IP157-001

The mean trough concentrations varied from 309.6 ng/dL to 389.8 ng/dL from 3rd injection through injection 8.

## 6. SAFETY EXPERIENCE ACROSS DEVELOPMENT

### 6.1. Extent of Exposure to Testosterone Undecanoate in Clinical Development

Across the TU development program, there were 3,556 subjects treated with 750 or 1000 mg of TU (Table 15). Of these, 725 were treated in the US and European Clinical Studies, which form the primary study grouping for general safety evaluation. All of the trials in this grouping studied hypogonadal men receiving TU as monotherapy and included comprehensive assessment of AEs. An additional 407 healthy males were treated with TU (750 and 1000 mg) in contraception clinical trials. Finally, 2424 hypogonadal men were treated with 1000 mg of TU in postmarketing studies. All of these studies were EU postmarketing studies that captured adverse drug reactions (ADRs). The largest study (IPASS [NE0601]) with 1438 patients emphasized collection of AEs of special interest including POME and hypersensitivity/anaphylactic reactions. The male contraception studies and postmarketing studies were included in the assessment of POME and anaphylaxis.

Overall, the clinical trial experience with TU was of long-duration, which allows for a full description of the safety profile. Median study duration in most study groupings often approached or even exceeded 2 years. In the primary study grouping of US and EU Clinical Studies, median study duration was 22.5 months. The demographic characteristics of the men in the US and European Clinical Studies are shown in Table 16. The mean age ( $\pm$ SD) was 51.9  $\pm$  12.3 years and the mean weight was 99  $\pm$  19.8 kg. The majority of men were under age 65 (86.3%), from the United States (72.3%), and white (87%).

**Table 15: Number of Subjects and Person Years of Exposure by Study Grouping (n=3556)**

	TU 750 MG			TU 1000 MG			Overall		
	N	Total Person-Year	Median Duration (Weeks)	N	Total Person-Year	Median Duration (Weeks)	N	Total Person-Year	Median Duration (Weeks)
<b>US and EU Clinical Studies Combined</b>	272	475.5	84.1	453	957.8	98.0	725	1433.3	90.3
<b>US Clinical Study:</b> IP157-001 All Parts	272	475.5	84.1	252	473.6	90.9	524	949.1	89.9
<b>US Clinical Study:</b> IP157-001 Parts C & C2 Only	153	200.9	83.9	0	0	0	153	200.9	83.9
<b>EU Clinical Studies:</b> JPH01495, JPH04995, ME98096, ME97029, 306605, 303934	0	0	0	201	484.2	150.0	201	484.2	150.0
<b>EU Male Contraception Studies:</b> 97028, 97173, 98016, 99015, 42306	195	142.7	40.3	212	137.6	39.5	407	280.3	40.1
<b>EU Postmarketing Studies:</b> 39732 (NEO601 IPASS), AWB0105, Czech NEO, NB02, TG09, and 14853	0	0	0	2424	2508.3	55.9	2424	2508.3	55.9

Data Source: 5.3.5.3, AVEED ISS [Table 1.2, Table 2.2, Table 3.2, Table 4.2, Table 5.2, and Table 6.1]

TU=Testosterone undecanoate

**Table 16: Demographic Characteristics of Subjects Treated with Testosterone Undecanoate in US and European Clinical Studies (n=725)**

	TU-750 mg (N=272)	TU-1000 mg (N=453)	Overall (N=725)
Age (years)			
n	272	453	725
Mean	54.4	50.4	51.9
Std. Dev	10.4	13.1	12.3
Median	54	52	53
Age Category			
18 to <65 Years	225 (82.7%)	401 (88.5%)	626 (86.3%)
≥65 Years	47 (17.3%)	52 (11.5%)	99 (13.7%)
Race			
White	215 (79.0%)	416 (91.8%)	631 (87.0%)
Black	31 (11.4%)	25 (5.5%)	56 (7.7%)
Hispanic	18 (6.6%)	9 (2.0%)	27 (3.7%)
Other	8 (2.9%)	3 (0.7%)	11 (1.5%)
Geographic Region			
US	272 (100%)	252 (55.6%)	524 (72.3%)
Ex-US	0	201 (44.4%)	201 (27.7%)
Baseline Weight (kg)			
n	270	451	721
Mean	101.9	97.2	99.0
Std. Dev.	18.4	20.4	19.8
Median	99.9	94.9	96.7

## 6.2. Summary of Treatment-Emergent Adverse Events

A high level summary of AE incidence by study grouping is shown in [Table 17](#). As is common in long-duration studies conducted during the pre-approval clinical development phase where capture of AEs is comprehensive, the incidence of subjects experiencing any AE during treatment was high, ranging from 72% to 96%. This is not the case in the postmarketing studies, which were designed to capture AEs with a suspected relationship to study medication (ADRs).

As expected, the incidence (14%-20%) of serious adverse events (SAEs) was higher in the middle-aged, hypogonadal men with multiple co-morbidities than in the younger, healthy men in the contraception studies (3%-4%). SAEs in the postmarketing studies were infrequent because only SAEs suspected to be related to study medication were captured.

Approximately 10% of hypogonadal men discontinued treatment due to an AE in the US and European clinical studies. A very low percentage of men dropped out of the postmarketing studies due to an AE, because the AE leading to withdrawal needed to have a suspected relationship to study medication to be included.

**Table 17: Overview of Treatment-Emergent Adverse Events by Study Grouping**

	US and EU Clinical Studies Combined	IP157-001 (All Parts)		EU Clinical Studies	Male Contraception Clinical Studies		PM Studies
	TU-750 + TU-1000 mg (N=725)	TU-750 mg (N=272)	TU-1000 mg (N=252)	TU-1000 mg (N=201)	TU-750 mg + Adj Ther (N=195)	TU-1000 mg + Adj Ther (N=212)	TU-1000 mg (N=2424)
At Least 1 TEAE	538 (74.2%)	198 (72.8%)	195 (77.4%)	145 (72.1%)	188 (96.4%)	185 (87.3%)	197 (8.1%)
At Least 1 SAE	116 (16.0%)	38 (14.0%)	37 (14.7%)	41 (20.4%)	5 (2.6%)	9 (4.2%)	15 (0.6%)
At Least 1 TEAE Leading to Discontinuation of Study Drug	65 (9.0%)	29 (10.7%)	27 (10.7%)	9 (4.5%)	21 (10.8%)	12 (5.7%)	45 (1.9%)
Cumulative Exposure to TU in Person-Years <sup>a</sup>	1433.3	475.5	473.6	484.2	142.7	137.6	2508.3

Data Source: 5.3.5.3, AVEED ISS

SAE=Serious adverse event; TEAE=Treatment-emergent adverse event; TU=Testosterone undecanoate

### 6.3. Treatment-Emergent Adverse Events

Treatment-emergent AEs that were reported in at least 3% of subjects in the US and European clinical studies are shown in [Table 18](#). These AEs were typical of those observed in subjects in clinical trials, in general, and of those receiving IM testosterone replacement therapy, in particular. Respiratory tract symptoms are frequently reported in clinical trials. In these trials that includes nasopharyngitis (8.6%), upper respiratory tract (URT) infection (4.8%), sinusitis (4.7%), and bronchitis (3.7%). Headache is also common and was reported in 4.1% of subjects in these trials. Injection site pain is common in trials of IM-administered products and was reported in 4.6% of subjects in these trials. Most reports of injection site pain were mild or moderate in severity as shown in greater detail for all injection site events in [Table 19](#). Severe injection site events were infrequent (0.4%). Hypertension (5.0%), prostatitis (4.7%), increased prostate-specific antigen (PSA) (4.8%), acne (3.3%), and sleep apnea syndrome (2.2%) are commonly reported with other TRTs and were seen in these trials.

The incidence of increased PSA was inflated by protocol design because PSA was measured at almost every visit in both, the US and European clinical studies. In some studies a threshold was imposed for withdrawing patients due to an elevated test result. Of the 35 (4.6%) subjects with increased PSA, none of the events were serious and 6 subjects withdrew from the trials because of this event. Of these 6 subjects, the elevated PSA values ranged from 3.39 to 8.51 ng/mL at the

patients' last visit. Two (2) subjects were found to have prostate cancer as a result of investigating the increased PSA. Of the 4 other subjects, 1 had prostatitis, 1 had prostatic dysplasia, and the remaining 2 did not have any other prostate condition recorded on their case report form.

Symptoms related to benign prostatic hypertrophy (BPH) are common both in men of this age and in men receiving TRT because the prostate gland is a testosterone responsive organ. Overall, 3.3% (24) of men experienced 1 or more symptoms associated with BPH (nocturia, pollakiuria, urine flow decreased, urinary retention, or urinary hesitancy) in the US and European clinical studies. There was no evidence that symptomatology increased in frequency with longer exposure to testosterone undecanoate (Table 20).

Other AEs often associated with TRTs were seen at lower incidences. For example, increased triglycerides (2.1%), increased hemoglobin (1.8%), and gynaecomastia (0.3%) have all been reported with other TRTs and were seen at low incidences in these long-duration clinical trials.

When reviewing laboratory tests obtained during the trials, increased triglycerides levels of potential clinical significance occurred in 1.2% of subjects receiving 750 mg of testosterone undecanoate who had non-potentially clinically significant values at study entry (Table 21). Increased hemoglobin levels of potential clinical significance were not observed in any subjects receiving 750 mg of testosterone undecanoate who had non-potentially clinically significant values at study entry (Table 21). Although there are limitations to comparing AE rates across studies and drugs, an informal comparison to other TRT therapies based on information in the US Prescribing Information shows that the rates of a number of these AEs are similar to recently approved testosterone products in the United States when comparing similar durations of treatment (see Table 37).

**Table 18: Incidence of Treatment-Emergent Adverse Events That Occurred in At Least 3% of the Population in US and EU Clinical Trials**

MedDRA SOC (Body System)/ Preferred Term	TU-750 mg (N=272)	TU-1000 mg (N=453)	Overall (N=725)
At least one treatment-emergent adverse event	198 (72.8%)	340 (75.1%)	538 (74.2%)
Infections and infestations	84 (30.9%)	155 (34.2%)	239 (33.0%)
Nasopharyngitis	14 (5.1%)	48 (10.6%)	62 (8.6%)
Upper respiratory tract infection	15 (5.5%)	20 (4.4%)	35 (4.8%)
Sinusitis	19 (7.0%)	15 (3.3%)	34 (4.7%)
Bronchitis	12 (4.4%)	15 (3.3%)	27 (3.7%)
Urinary tract infection	6 (2.2%)	14 (3.1%)	20 (2.8%)
Musculoskeletal and connective tissue disorders	53 (19.5%)	97 (21.4%)	150 (20.7%)
Back pain	13 (4.8%)	19 (4.2%)	32 (4.4%)
Arthralgia	12 (4.4%)	19 (4.2%)	31 (4.3%)
Musculoskeletal pain	6 (2.2%)	14 (3.1%)	20 (2.8%)
Pain in extremity	9 (3.3%)	11 (2.4%)	20 (2.8%)
Investigations	51 (18.8%)	87 (19.2%)	138 (19.0%)
Prostatic specific antigen increased	20 (7.4%)	15 (3.3%)	35 (4.8%)
General disorders and administration site conditions	50 (18.4%)	58 (12.8%)	108 (14.9%)
Injection site pain	10 (3.7%)	23 (5.1%)	33 (4.6%)
Fatigue	17 (6.3%)	8 (1.8%)	25 (3.4%)
Reproductive system and breast disorders	43 (15.8%)	65 (14.3%)	108 (14.9%)
Prostatitis	15 (5.5%)	19 (4.2%)	34 (4.7%)
Gastrointestinal disorders	32 (11.8%)	75 (16.6%)	107 (14.8%)
Diarrhoea	4 (1.5%)	19 (4.2%)	23 (3.2%)
Nervous system disorders	28 (10.3%)	70 (15.5%)	98 (13.5%)
Headache	6 (2.2%)	24 (5.3%)	30 (4.1%)
Skin and subcutaneous tissue disorders	29 (10.7%)	56 (12.4%)	85 (11.7%)
Acne	9 (3.3%)	15 (3.3%)	24 (3.3%)
Psychiatric disorders	34 (12.5%)	50 (11.0%)	84 (11.6%)
Insomnia	12 (4.4%)	13 (2.9%)	25 (3.4%)
Respiratory, thoracic and mediastinal disorders	29 (10.7%)	35 (7.7%)	64 (8.8%)
Sleep apnoea syndrome	10 (3.7%)	6 (1.3%)	16 (2.2%)
Vascular disorders	23 (8.5%)	37 (8.2%)	60 (8.3%)
Hypertension	16 (5.9%)	20 (4.4%)	36 (5.0%)

**Table 19: Incidence of Treatment-Emergent Adverse Events of Injection Site Reactions in Subjects Treated with Testosterone Undecanoate in Study IP157-001 and European Clinical Studies**

MedDRA SOC(Body System)/ Preferred Term	Number (%) of Patients								
	TU-750 mg (N=272)			TU-1000 mg (N=453)			Overall (N=725)		
	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
At least one treatment-emergent adverse event	13 (4.8%)	3 (1.1%)	0	21 (4.6%)	4 (0.9%)	3 (0.7%)	34 (4.7%)	7 (1.0%)	3 (0.4%)
General disorders and administration site conditions	13 (4.8%)	3 (1.1%)	0	21 (4.6%)	4 (0.9%)	3 (0.7%)	34 (4.7%)	7 (1.0%)	3 (0.4%)
Injection site pain	8 (2.9%)	2 (0.7%)	0	16 (3.5%)	4 (0.9%)	3 (0.7%)	24 (3.3%)	6 (0.8%)	3 (0.4%)
Injection site discomfort	0	0	0	3 (0.7%)	0	0	3 (0.4%)	0	0
Injection site erythema	2 (0.7%)	0	0	2 (0.4%)	2 (0.4%)	0	4 (0.6%)	2 (0.3%)	0
Injection site haematoma	0	0	0	1 (0.2%)	0	0	1 (0.1%)	0	0
Injection site haemorrhage	0	1 (0.4%)	0	0	0	0	0	1 (0.1%)	0
Injection site induration	0	0	0	0	1 (0.2%)	0	0	1 (0.1%)	0
Injection site paraesthesia	0	0	0	1 (0.2%)	0	0	1 (0.1%)	0	0
Injection site pruritus	2 (0.7%)	0	0	2 (0.4%)	0	0	4 (0.6%)	0	0
Injection site rash	2 (0.7%)	0	0	0	0	0	2 (0.3%)	0	0
Injection site swelling	3 (1.1%)	0	0	3 (0.7%)	1 (0.2%)	0	6 (0.8%)	1 (0.1%)	0

**Table 20: Incidence of Treatment-Emergent Adverse Events Related to Benign Prostatic Hyperplasia in Subjects Treated with Testosterone Undecanoate in Study IP157-001 and European Clinical Studies**

Treatment-Emergent Adverse Event	0-6 Months (N=725)	6-12 Months (N=635)	12-18 Months (N=573)	18-24 Months (N=513)	Overall US and EU (n=725)
BPH symptomatology (AUA criteria <sup>a</sup> )	8 (1.1%)	9 (1.4%)	6 (1.0%)	1 (0.2%)	24 (3.3%)
Nocturia	3 (0.4%)	1 (0.2%)	0	1 (0.2%)	5 (0.7%)
Pollakiuria	2 (0.3%)	3 (0.5%)	4 (0.7%)	0	10 (1.4%)
Urine flow decreased	2 (0.3%)	3 (0.5%)	1 (0.2%)	0	6 (0.8%)
Urinary retention	1 (0.1%)	3 (0.5%)	1 (0.2%)	0	6 (0.8%)
Urinary hesitation	0	0	0	0	2 (0.3%)

<sup>a</sup> Based on American Urological Association (AUA) Benign Prostatic Hyperplasia (BPH) Symptom Score (AUA Clinical Guideline, Management of BPH [Revised, 2010]; <http://www.auanet.org/content/clinical-practice-guidelines/clinical-guidelines.cfm?sub=bph>; accessed 11-Feb-2013)

**Table 21: Potentially Clinically Significant Shifts from Baseline – Triglycerides and Hemoglobin (Study IP157-001: Part C)**

Parameter	PCS Criteria	Baseline PCS	750 mg (N=130) Post-Baseline PCS		
			Low	No PCS	High
Triglycerides, fasting		Low	--	--	--
		No PCS (n=82)	0	81 (98.8%)	1 (1.2%)
	>600 mg/dL	High (n=0)	0	0	0
Hemoglobin	≤11.5 g/dL	Low (n=2)	0	2 (100.0%)	0
		No PCS (n=124)	2 (1.6%)	122 (98.4%)	0
	>20 g/dL	High (n=0)	0	0	0

PCS=Potentially clinically significant

#### 6.4. Adverse Events Associated with Study Discontinuation

Overall in these long-duration US and European clinical studies, 9.0% of subjects had AEs associated with study discontinuation (Table 22). The most common AEs associated with study discontinuation were prostate cancer (1.0%) and increased PSA (0.8%). Subjects with prostate cancer are reviewed in more detail in section 6.5 that examines SAEs. The incidence of increased PSA was partially influenced by protocol design as discussed previously.

**Table 22: Incidence of Treatment-Emergent Adverse Events that Led to Discontinuation in US and EU Clinical Studies**

MedDRA SOC (Body System)/ Preferred Term	TU-750 mg (N=272)	TU-1000 mg (N=453)	Overall (N=725)
At Least One Treatment-Emergent Adverse Event That Led to Discontinuation of Study Drug	29 (10.7%)	36 (7.9%)	65 (9.0%)
Investigations	10 (3.7%)	8 (1.8%)	18 (2.5%)
Prostatic specific antigen increased	5 (1.8%)	1 (0.2%)	6 (0.8%)
Haemoglobin increased	2 (0.7%)	2 (0.4%)	4 (0.6%)
Haematocrit increased	2 (0.7%)	1 (0.2%)	3 (0.4%)
Oestradiol increased	1 (0.4%)	2 (0.4%)	3 (0.4%)
Blood creatine phosphokinase increased	0	2 (0.4%)	2 (0.3%)
Red blood cell count increased	1 (0.4%)	1 (0.2%)	2 (0.3%)
Basophil count abnormal	1 (0.4%)	0	1 (0.1%)
Blood testosterone free increased	0	1 (0.2%)	1 (0.1%)
Blood testosterone increased	0	1 (0.2%)	1 (0.1%)
Lymphocyte morphology abnormal	1 (0.4%)	0	1 (0.1%)
Prostatic specific antigen abnormal	0	1 (0.2%)	1 (0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (1.8%)	10 (2.2%)	15 (2.1%)
Prostate cancer	4 (1.5%)	3 (0.7%)	7 (1.0%)
Pancreatic carcinoma	0	2 (0.4%)	2 (0.3%)
Bladder cancer	1 (0.4%)	0	1 (0.1%)
Colon cancer	0	1 (0.2%)	1 (0.1%)
Hepatic neoplasm malignant	0	1 (0.2%)	1 (0.1%)
Laryngeal cancer	0	1 (0.2%)	1 (0.1%)
Lung neoplasm malignant	0	1 (0.2%)	1 (0.1%)
Neoplasm prostate	0	1 (0.2%)	1 (0.1%)
Reproductive system and breast disorders	4 (1.5%)	4 (0.9%)	8 (1.1%)
Prostatic dysplasia	3 (1.1%)	1 (0.2%)	4 (0.6%)
Prostatitis	0	2 (0.4%)	2 (0.3%)
Breast pain	0	1 (0.2%)	1 (0.1%)
Prostatomegaly	1 (0.4%)	0	1 (0.1%)
Testicular atrophy	1 (0.4%)	0	1 (0.1%)
Psychiatric disorders	3 (1.1%)	3 (0.7%)	6 (0.8%)
Anxiety	2 (0.7%)	0	2 (0.3%)
Mood swings	2 (0.7%)	0	2 (0.3%)
Agitation	0	1 (0.2%)	1 (0.1%)
Bipolar disorder	0	1 (0.2%)	1 (0.1%)
Depression	0	1 (0.2%)	1 (0.1%)
Insomnia	1 (0.4%)	0	1 (0.1%)

**Table 22: Incidence of Treatment-Emergent Adverse Events that Led to Discontinuation in US and EU Clinical Studies (Continued)**

MedDRA SOC (Body System)/ Preferred Term	TU-750 mg (N=272)	TU-1000 mg (N=453)	Overall (N=725)
Cardiac disorders	3 (1.1%)	2 (0.4%)	5 (0.7%)
Myocardial infarction	2 (0.7%)	2 (0.4%)	4 (0.6%)
Cardiac arrest	1 (0.4%)	0	1 (0.1%)
Musculoskeletal and connective tissue disorders	2 (0.7%)	1 (0.2%)	3 (0.4%)
Back pain	1 (0.4%)	0	1 (0.1%)
Lumbar spinal stenosis	1 (0.4%)	0	1 (0.1%)
Osteoarthritis	0	1 (0.2%)	1 (0.1%)
Pain in extremity	1 (0.4%)	0	1 (0.1%)
Nervous system disorders	0	3 (0.7%)	3 (0.4%)
Burning sensation	0	1 (0.2%)	1 (0.1%)
Cerebrovascular accident	0	1 (0.2%)	1 (0.1%)
Reversible ischaemic neurological deficit	0	1 (0.2%)	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	1 (0.4%)	2 (0.4%)	3 (0.4%)
Dyspnoea	0	1 (0.2%)	1 (0.1%)
Nasal congestion	0	1 (0.2%)	1 (0.1%)
Sleep apnoea syndrome	1 (0.4%)	0	1 (0.1%)
Blood and lymphatic system disorders	1 (0.4%)	1 (0.2%)	2 (0.3%)
Polycythaemia	1 (0.4%)	1 (0.2%)	2 (0.3%)
Gastrointestinal disorders	1 (0.4%)	1 (0.2%)	2 (0.3%)
Dyspepsia	0	1 (0.2%)	1 (0.1%)
Irritable bowel syndrome	1 (0.4%)	0	1 (0.1%)
Infections and infestations	1 (0.4%)	1 (0.2%)	2 (0.3%)
Device related infection	0	1 (0.2%)	1 (0.1%)
Sepsis	1 (0.4%)	0	1 (0.1%)
Injury, poisoning and procedural complications	2 (0.7%)	0	2 (0.3%)
Heat exhaustion	1 (0.4%)	0	1 (0.1%)
Stab wound	1 (0.4%)	0	1 (0.1%)
Skin and subcutaneous tissue disorders	1 (0.4%)	1 (0.2%)	2 (0.3%)
Acne	1 (0.4%)	0	1 (0.1%)
Skin ulcer	0	1 (0.2%)	1 (0.1%)
Metabolism and nutrition disorders	0	1 (0.2%)	1 (0.1%)
Diabetes mellitus	0	1 (0.2%)	1 (0.1%)
Renal and urinary disorders	0	1 (0.2%)	1 (0.1%)
Renal mass	0	1 (0.2%)	1 (0.1%)
Vascular disorders	1 (0.4%)	0	1 (0.1%)
Deep vein thrombosis	1 (0.4%)	0	1 (0.1%)

Data Source: ISS Table 4.3.11

## 6.5. Deaths and Serious Adverse Events

There were 7 (0.97%) subjects out of the 725 subjects in the US and EU clinical studies who had treatment-emergent AEs associated with death. A summary of each patient who died is shown in [Table 23](#). The AEs associated with death were 1 subject each with stab wound, cardiac arrest, myocardial infarction, pneumonia, cerebrovascular accident, malignant lung neoplasm, and road traffic accident. All 7 deaths occurred at least 1 month after the last injection of TU and most events occurred 2 or more months after the last injection. None of the deaths occurred in proximity to an injection of TU and none were due to POME or anaphylaxis. In each subject, the investigator indicated that the event leading to death was unrelated to TU.

No deaths occurred in the male contraception studies. Two (2) deaths were reported in the postmarketing studies and those are summarized in [Table 24](#). One (1) patient died of a completed suicide and the other died of multi-organ failure (associated with staphylococcal sepsis). Neither of the deaths occurred in proximity to an injection of TU and none were due to POME or anaphylaxis. In each subject, the investigator indicated that the event leading to death was unrelated to TU.

A full narrative for each death in the US and EU clinical studies and in the postmarketing studies is provided in [Appendix 2](#).

At the time of the data cut-off on November 25, 2011, Bayer Pharmaceuticals had received reports of 14 deaths of patients who from around the world during the marketing experience with TU. This was at the time that more than 3.1 million doses had been sold worldwide. A summary of the events leading to death is shown in [Table 25](#). Twelve (12) of the deaths occurred in patients participating in investigator-initiated studies and the remaining 2 deaths were reported spontaneously. Of the 12 deaths in patients participating in investigator-initiated studies, 8 occurred in patients receiving TU and 4 occurred in patients receiving placebo or no study medication. In all 12 cases where the patients were enrolled in a study, the investigators did not consider the fatal events to be related to study medication.

Of the deaths on active drug, 2 of the deaths were accidental, 2 were due to cancer, 1 had an unknown cause, and 1 each was due to suicide, asphyxia, and sepsis. One (1) death due to myocardial infarction occurred on the same day of the patient's last injection of TU, but the exact time is not known as it was not observed by the investigator-physician. More information is being sought about this case. One (1) death due to complications of pulmonary hypertension was in a patient with a known history of pulmonary hypertension that preceded the start of TU therapy. This death occurred approximately 3 years after the last dose of TU.

**Table 23: Summary of Patients Who Died in the Testosterone Undecanoate US and EU Clinical Studies**

Study No.	Subject No.	Treatment	Age (y)/ Race	System Organ Class/Preferred Term (Verbatim Term)	Last Treatment Date	AE Onset Date/Time	AE Stop Date/Time	Severity	Investigator-Attributed Relationship to Study Drug
306605	01615-000067	TU 1000 mg	58/ White	Infections And Infestations/ Pneumonia (Pneumonia)	-- <sup>a</sup>	(b) (6)		Severe	Unrelated
IP157-001A	00070-004006	TU 750 mg	54/ White	Injury, Poisoning and Procedural Complications/ Stab Wound (Stab Wounds)	11-Aug-2006	(b) (6)	(b) (6)	Severe	Unrelated
IP157-001A	00078-004162	TU 1000 mg	68/ White	Nervous System Disorders/ Cerebrovascular Accident (Massive Stroke)	29-Jan-2008	(b) (6)	(b) (6)	Severe	Unrelated
IP157-001B	00001-006020	TU 1000 mg	75/ White	Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)/ Lung Neoplasm Malignant (Malignant Neoplasm of Lung)	11-Jan-2007	(b) (6)		Severe	Unrelated
IP157-001C	00050-007010	TU 750 mg	50/ White	Cardiac Disorders/ Cardiac Arrest (Cardiac Arrest)	6-Feb-2008	(b) (6)	(b) (6)	Severe	Unrelated
IP157-001C	00078-007012	TU 750 mg	45/ Black	Cardiac Disorders/ Myocardial Infarction (Fatal MI)	24-Sep-2007	(b) (6)	(b) (6)	Severe	Unrelated
ME97029	00001-000039	TU 1000 mg	24/ White	Injury, Poisoning and Procedural Complications/ Road Traffic Accident (Traffic Accident; Pat. was riding a motor cycle, lost power over the cycle and collided with a truck)	28-May-1999	(b) (6) / 11:00		Severe	Unrelated

Data Source 5.3.5.3 ISS

<sup>a</sup> Event occurred 1.5 years after first administration of the study drug (TU) and 1 month after the last injection of TU.

AE=Adverse event; MI= Myocardial Infarction; TU=Testosterone undecanoate

Note: "Last Treatment Date" was obtained from Case Report Forms (CRFs) for subject 00001-000039 and from death narratives for remaining subjects

**Table 24: Summary of Patients Who Died in Postmarketing Surveillance Studies**

Study No.	Subject No.	Treatment	Age (y)/ Race	System Organ Class/Preferred Term (Verbatim Term)	Last Treatment Date	AE Onset Date/Time	AE Stop Date/Time	Severity	Investigator-Attributed Relationship to Study Drug
IPASS	00103-002051	TU 1000 mg	56/ White	Psychiatric Disorders/ Completed Suicide (Suicide, Cause Unknown)	6-Aug-2007	(b) (6)		Severe	Unrelated
NB02	00001-000012	TU 1000 mg	62/ Not Collected	General Disorders and Administration Site Conditions/ Multi-Organ Failure (Multiorgan Failure)	27-Mar-2007	(b) (6)		Severe	Unrelated
				Infections and Infestations/ Staphylococcal Sepsis (Fatal Staphylococcus Aureus Sepsis [LLT: Staphylococcus Aureus Septicaemia])	27-Mar-2007	(b) (6)		Severe	Unrelated

Data Source 5.3.5.3 ISS

AE=Adverse event; TU=Testosterone undecanoate

**Table 25: Summary of Deaths Reported During the Marketing Experience with Testosterone Undecanoate (Through November 25, 2011)**

Case ID	Age (y)	Treatment	Product Start Date	Product End Date	AE Preferred Term	AE Onset Date	AE Stop Date <sup>a</sup>	IIS <sup>b</sup>
RU-2006-040688	64	Placebo	10-Aug-2006	21-Sep-2006	Myocardial infarction	29-Nov-2006	30-Nov-2006	Yes
200820628GPV	61	Reandron <sup>c</sup>	28-Mar-2007	20-Sep-2007	Road traffic accident	11-Oct-2007	11-Oct-2007	Yes
200916880GPV	70	Placebo	UNK	UNK	Death	2007	2007	Yes
200916887GPV	52	Nebido	1-Aug-2006	17-Jul-2007	Death	20-Nov-2007 <sup>d</sup>	20-Nov-2007 <sup>d</sup>	Yes
200911275BNE	72	No study medication	N/A	N/A	Acute myocardial infarction	31-Mar-2009	31-Mar-2009	Yes
200922706GPV	71	Nebido	30-Mar-2009	18-May-2009	Asphyxia	30-May-2009	30-May-2009	No
200933904GPV	61	Nebido	12-Dec-2008	31-Jan-2009	Bile duct cancer non-resectable	4-Apr-2009	23-Sep-2009	Yes
200935090GPV	51	Placebo	19-Oct-2008	09-Aug-2009	Myocardial infarction	04-Sep-2009	04-Sep-2009	Yes
200933909GPV	70	Nebido	27-Jan-2009	27-May-2009	Colon cancer	3-Aug-2009	18-Oct-2009	Yes
201042256GPV	31	Nebido	12-Jun-2009	16-Oct-2009	Completed suicide	(b) (6)	(b) (6)	Yes
201012899GPV	43	Nebido	15-Feb-2009	13-Dec-2009	Acute myocardial infarction	13-Dec-2009	13-Dec-2009	Yes
SE-2007-002541	64	Nebido	16-Dec-2005	10-Oct-2006	Pulmonary hypertension	2009	2009	No
201039452GPV	71	Nebido	UNK	UNK	Sepsis	31-Jun-2010	17-Aug-2010	Yes
2011-058701	61	Nebido	26-Nov-2010	17-Jun-2011	Cardiac arrest	30-Jun-2011	30-Jun-2011	Yes

<sup>a</sup> Date of death

<sup>b</sup> These events were reported to Bayer from investigators who were conducting investigator-initiated studies (IIS) of testosterone undecanoate.

<sup>c</sup> Reandron is the trade name for Nebido in Australia

<sup>d</sup> Investigator informed of death on that date

AE=Adverse event; N/A=Not applicable; UNK=Unknown

At least 1 treatment-emergent SAE occurred in 16.0% of subjects treated with TU in the US and European clinical studies (Table 26). The most frequent treatment-emergent SAEs were prostate cancer (1.0%), myocardial infarction (1.0%), osteoarthritis (0.8%), and coronary artery disease (CAD) (0.7%).

All 7 cases of prostate cancer were diagnosed in the US clinical study (IP157-001). Four (4) cases were detected following evaluation of an elevated PSA level that was obtained based on the protocol-required testing schedule. Two (2) cases were in men with elevated PSA levels at baseline, although their screening values met the study entry criteria. The 7th subject had known prostate cancer at time of study entry but did not disclose it at the screening visit in violation of the entry criteria; he should have been excluded from the study. The fact that no cases of prostate cancer were observed during the other studies from Europe is likely based on an important demographic difference. The American men were on average almost 10 years older than the European men (mean age of  $55 \pm 11$  years vs  $45 \pm 14$  years). The strongest risk factor for prostate cancer is older age. The mean age of the 7 men with prostate cancer was  $65 \pm 11$  years.

All 7 subjects who experienced myocardial infarction either had a history of CAD or 1 or more risk factors for coronary disease. Six (6) subjects had hyperlipidemia, 6 had hypertension, 1 had type 2 diabetes mellitus, 2 were smokers, and 2 were obese. Six (6) subjects underwent coronary angiography and 5 subjects were revascularized while a 6th subject did not have any stenotic lesions. These 6 subjects recovered and the 7th subject had a fatal outcome. Four (4) of the 7 subjects were discontinued from TU therapy. In all cases, the investigators did not causally relate the events of myocardial infarction to the study medication.

Five (5) additional subjects experienced non-myocardial infarction events related to CAD. These were episodes of chest pain, angina pectoris, or abnormal cardiac stress test results. Three (3) subjects each had pre-existing CAD, hypertension, or hyperlipidemia and 2 had type 2 diabetes mellitus. None of the cases were associated with an increased hemoglobin level. Four (4) of the 5 subjects underwent coronary revascularization and all recovered from the index event. Most (4) of these subjects remained on TU therapy. In all cases, the investigators did not causally relate the events of CAD to the study medication.

The 6 cases of osteoarthritis all were individuals with joint disease who underwent joint (hip or knee) replacement during the course of the trials. All of them recovered and all remained on TU therapy.

**Table 26: Treatment-Emergent Serious Adverse Event: US and EU Clinical Studies (Two or More Subjects with Adverse Events in Overall Testosterone Undecanoate Exposure)**

MedDRA SOC (Body System)/ Preferred Term	TU-750 mg (N=272)	TU-1000 mg (N=453)	Overall (N=725)
At Least One Treatment-Emergent Serious Adverse Event	38 (14.0%)	78 (17.2%)	116 (16.0%)
Investigations	0	5 (1.1%)	5 (0.7%)
White blood cell count decreased	0	2 (0.4%)	2 (0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (2.2%)	11 (2.4%)	17 (2.3%)
Prostate cancer	4 (1.5%)	3 (0.7%)	7 (1.0%)
Pancreatic carcinoma	0	2 (0.4%)	2 (0.3%)
General disorders and administration site conditions	2 (0.7%)	3 (0.7%)	5 (0.7%)
Non-cardiac chest pain	0	2 (0.4%)	2 (0.3%)
Infections and infestations	6 (2.2%)	11 (2.4%)	17 (2.3%)
Urinary tract infection	1 (0.4%)	2 (0.4%)	3 (0.4%)
Sepsis	1 (0.4%)	1 (0.2%)	2 (0.3%)
Reproductive system and breast disorders	1 (0.4%)	4 (0.9%)	5 (0.7%)
Prostatitis	1 (0.4%)	3 (0.7%)	4 (0.6%)
Cardiac disorders	8 (2.9%)	11 (2.4%)	19 (2.6%)
Myocardial infarction <sup>a</sup>	3 (1.1%)	4 (0.9%)	7 (1.0%)
Coronary artery disease	1 (0.4%)	4 (0.9%)	5 (0.7%)
Atrial fibrillation	2 (0.7%)	1 (0.2%)	3 (0.4%)
Cardiac arrest	1 (0.4%)	1 (0.2%)	2 (0.3%)
Cardiac failure congestive	1 (0.4%)	1 (0.2%)	2 (0.3%)
Gastrointestinal disorders	5 (1.8%)	7 (1.5%)	12 (1.7%)
Diverticulum intestinal	1 (0.4%)	1 (0.2%)	2 (0.3%)
Inguinal hernia	0	2 (0.4%)	2 (0.3%)
Injury, poisoning and procedural complications	2 (0.7%)	10 (2.2%)	12 (1.7%)
Road traffic accident	0	2 (0.4%)	2 (0.3%)
Wound dehiscence	0	2 (0.4%)	2 (0.3%)
Musculoskeletal and connective tissue disorders	9 (3.3%)	13 (2.9%)	22 (3.0%)
Osteoarthritis	1 (0.4%)	5 (1.1%)	6 (0.8%)
Spinal column stenosis	3 (1.1%)	1 (0.2%)	4 (0.6%)
Cervical spinal stenosis	2 (0.7%)	1 (0.2%)	3 (0.4%)
Arthritis	0	2 (0.4%)	2 (0.3%)
Intervertebral disc disorder	2 (0.7%)	0	2 (0.3%)

**Table 26: Treatment-Emergent Serious Adverse Event: US and EU Clinical Studies (Two or More Subjects with Adverse Events in Overall Testosterone Undecanoate Exposure) (Continued)**

MedDRA SOC (Body System)/ Preferred Term	TU-750 mg (N=272)	TU-1000 mg (N=453)	Overall (N=725)
Nervous system disorders	1 (0.4%)	10 (2.2%)	11 (1.5%)
Cerebrovascular accident	1 (0.4%)	2 (0.4%)	3 (0.4%)
Convulsion	0	2 (0.4%)	2 (0.3%)
Syncope	0	2 (0.4%)	2 (0.3%)
Renal and urinary disorders	0	6 (1.3%)	6 (0.8%)
Nephrolithiasis	0	2 (0.4%)	2 (0.3%)
Surgical and medical procedures	0	4 (0.9%)	4 (0.6%)
Knee arthroplasty	0	2 (0.4%)	2 (0.3%)

Data Source: ISS Table 4.3.9

<sup>a</sup> Includes events coded to “acute myocardial infarction”

## 6.6. Treatment-Emergent Adverse Events with Long-Term Use

The incidence of treatment-emergent AEs was examined by duration of use for all AEs present at an incidence of 3% or more in the US and European clinical studies (Table 27). The incidences of AEs were stable across the time strata and do not suggest an increase in any AE with longer duration of use.

**Table 27: Incidence of Treatment-Emergent Adverse Events Stratified by the Subinterval in US and EU Clinical Studies**

MedDRA SOC(Body System)/ Preferred Term	Number (%) of Patients				
	0-6 Months (N=725)	6-12 Months (N=635)	12-18 Months (N=573)	18-24 Months (N=513)	After 24 Months (N=297)
At Least One Treatment-Emergent Adverse Event	338 (46.6%)	272 (42.8%)	211 (36.8%)	125 (24.4%)	149 (50.2%)
Infections and infestations	90 (12.4%)	87 (13.7%)	52 (9.1%)	42 (8.2%)	53 (17.8%)
Nasopharyngitis	22 (3.0%)	18 (2.8%)	8 (1.4%)	12 (2.3%)	13 (4.4%)
Bronchitis	10 (1.4%)	8 (1.3%)	7 (1.2%)	3 (0.6%)	2 (0.7%)
Upper respiratory tract infection	10 (1.4%)	13 (2.0%)	5 (0.9%)	5 (1.0%)	8 (2.7%)
Sinusitis	7 (1.0%)	11 (1.7%)	5 (0.9%)	6 (1.2%)	10 (3.4%)
Urinary tract infection	6 (0.8%)	9 (1.4%)	1 (0.2%)	3 (0.6%)	5 (1.7%)
General disorders and administration site conditions	70 (9.7%)	18 (2.8%)	21 (3.7%)	8 (1.6%)	13 (4.4%)
Injection site pain	20 (2.8%)	3 (0.5%)	10 (1.7%)	3 (0.6%)	4 (1.3%)
Fatigue	18 (2.5%)	3 (0.5%)	3 (0.5%)	3 (0.6%)	3 (1.0%)
Musculoskeletal and connective tissue disorders	61 (8.4%)	59 (9.3%)	37 (6.5%)	15 (2.9%)	30 (10.1%)
Arthralgia	14 (1.9%)	11 (1.7%)	6 (1.0%)	3 (0.6%)	2 (0.7%)
Back pain	11 (1.5%)	10 (1.6%)	6 (1.0%)	2 (0.4%)	9 (3.0%)
Musculoskeletal pain	7 (1.0%)	4 (0.6%)	4 (0.7%)	1 (0.2%)	5 (1.7%)
Gastrointestinal disorders	50 (6.9%)	26 (4.1%)	14 (2.4%)	13 (2.5%)	22 (7.4%)
Diarrhoea	9 (1.2%)	6 (0.9%)	4 (0.7%)	3 (0.6%)	2 (0.7%)
Investigations	46 (6.3%)	42 (6.6%)	31 (5.4%)	20 (3.9%)	26 (8.8%)
Prostatic specific antigen increased	10 (1.4%)	12 (1.9%)	8 (1.4%)	9 (1.8%)	3 (1.0%)
Nervous system disorders	43 (5.9%)	26 (4.1%)	19 (3.3%)	10 (1.9%)	17 (5.7%)
Headache	19 (2.6%)	6 (0.9%)	7 (1.2%)	3 (0.6%)	4 (1.3%)
Psychiatric disorders	37 (5.1%)	24 (3.8%)	17 (3.0%)	9 (1.8%)	11 (3.7%)
Insomnia	12 (1.7%)	7 (1.1%)	4 (0.7%)	0	2 (0.7%)

**Table 27: Incidence of Treatment Emergent Adverse Events Stratified by the Subinterval in US and EU Clinical Studies (Continued)**

MedDRA SOC(Body System)/ Preferred Term	Number (%) of Patients				
	0-6 Months (N=725)	6-12 Months (N=635)	12-18 Months (N=573)	18-24 Months (N=513)	After 24 Months (N=297)
Reproductive system and breast disorders	35 (4.8%)	31 (4.9%)	30 (5.2%)	17 (3.3%)	14 (4.7%)
Prostatitis	10 (1.4%)	7 (1.1%)	11 (1.9%)	6 (1.2%)	4 (1.3%)
Respiratory, thoracic and mediastinal disorders	30 (4.1%)	12 (1.9%)	9 (1.6%)	9 (1.8%)	13 (4.4%)
Sleep apnoea syndrome	5 (0.7%)	2 (0.3%)	2 (0.3%)	5 (1.0%)	2 (0.7%)
Skin and subcutaneous tissue disorders	29 (4.0%)	27 (4.3%)	10 (1.7%)	9 (1.8%)	14 (4.7%)
Acne	11 (1.5%)	3 (0.5%)	6 (1.0%)	1 (0.2%)	3 (1.0%)
Vascular disorders	19 (2.6%)	16 (2.5%)	15 (2.6%)	11 (2.1%)	5 (1.7%)
Hypertension	7 (1.0%)	9 (1.4%)	11 (1.9%)	7 (1.4%)	2 (0.7%)

Note: Patients are counted once within each SOC (Body System) and Preferred Term. The missing AE onset dates are imputed to the dates of first injection. Partial AE onset dates are imputed to middle of month or year if day or month is missing. 0-6 months: AE started dates from the first injection to 182 day; 6-12 months: AE started from 183 day to 365 day; 12-18 months: AE started from 366 day to 547 days; 18-24 months: AE started from 548 day to 730 days; After 24 months: AE started after 730 days from the first injection; The group total (N) is calculated as to sum all subjects with either the last injection date + 71 days or any AE onset date is after the lower bond of the interval. MedDRA version 14.0

TU=Testosterone undecanoate

## 6.7. Summary

Safety data for TU are based on an extensive safety database of 18 completed clinical studies conducted in 3,556 subjects treated with TU. AE data from the US clinical study in hypogonadal men, European clinical studies in hypogonadal men, male contraception studies in healthy subjects, and postmarketing studies in hypogonadal men provide supportive evidence of the safety of TU. Overall, the clinical trial experience with TU was of long duration, which allows for a full description of the safety profile. Median study duration in most study groupings often approached or even exceeded 2 years. In the primary study grouping of US and EU clinical studies, median study duration was 22.5 months (90.3 weeks).

Furthermore, the clinical trial safety profile is supported by the extensive (>3.1 million doses sold) and long-term (since 2003) marketing experience with Nebido (TU 1000 mg), which is the same formulation of TU, dosed at 4 mL (1000 mg) rather than 3 mL (750 mg). In the 9 years since Nebido was first introduced, it has never been withdrawn for any reason, (inclusive of safety reasons) in any of the 94 countries in which it is approved. The European Medicines Agency (EMA) has reviewed the postmarketing data on POME and anaphylaxis and required that the marketing authorization holder (MAH) provide additional information in the prescribing information, advise physicians about proper injection technique, and collect more data on post-injection reactions during postmarketing studies as will be described in section 7.

Treatment-emergent AEs were typical of those observed in subjects in clinical trials, in general, and of those receiving IM testosterone replacement therapy, in particular. Respiratory tract symptoms are frequently reported in clinical trials. In these trials, that included nasopharyngitis (8.6%), URT infection (4.8%), sinusitis (4.7%), and bronchitis (3.7%). Headache is also common and was reported in 4.1% of subjects in these trials. Injection site pain is common in trials of IM-administered products and was reported in 4.6% of subjects in these trials. Most reports of injection site pain were mild or moderate in severity. Hypertension (5.0%), prostatitis (4.7%), increased PSA (4.8%), acne (3.3%), and sleep apnea syndrome (2.2%) are commonly reported with other TRTs and were seen in these trials. The incidence of increased PSA was inflated by protocol design because PSA was measured frequently during the clinical trials. Symptoms of BPH, common in middle-aged men and those receiving TRT, were observed in 3.3% of subjects. Other AEs often associated with TRTs were seen at lower incidences. For example, increased triglycerides (2.1%), increased hemoglobin (1.8%), and gynaecomastia (0.3%) have all been reported with other TRTs and were seen at low incidences in these long-duration clinical trials. When looked at as a function of time there was no evidence that any of the AEs increased with longer treatment duration.

Overall, in these long-duration US and European clinical studies, 9.0% of subjects had AEs associated with study discontinuation. The most common AEs associated with study discontinuation were prostate cancer (1.0%) and increased PSA (0.8%). Prostate cancer (1.0%), myocardial infarction (1.0%), and osteoarthritis (0.8%) were the most commonly reported serious AEs. The occurrence of prostate cancer was seen only in the United States and was likely influenced by the older age of the men. Increased PSA and prostate cancer have also been reported to have led to discontinuation with other TRTs. The few deaths that were observed were due to a range of causes that were not felt by the investigators to be related to TRT in each instance. None of the deaths occurred in proximity to the TU injections. Overall, the safety

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profile of TU is in keeping with that of other TRTs, particularly those administered by the IM route.

## 7. IMMEDIATE POST-INJECTION REACTIONS

### 7.1. Pulmonary Oil Microembolism

#### 7.1.1. Background

Much of what we know about POME comes from the radiology literature where oil-based contrast agents are used in procedures such as myelography and lymphangiography.(8,9) The term was coined after it was found that contrast agents could inadvertently enter the venous system and migrate to the pulmonary vasculature. Two (2) mechanisms of venous access are known; lymphatic-venous communications in the case of lymphangiography and direct venous access in the case of myelography and during intramuscular injection.

Direct venous access has been demonstrated with Pantopaque, an oil-based contrast medium used for myelography. Because Pantopaque is poorly absorbed, the standard diagnostic approach is to aspirate the remaining contrast after the myelogram via a lumbar puncture. There are reports where the lumbar puncture was bloody and during the procedure the patient experienced an episode of “violent, uncontrollable coughing” which lasted for ≈30 minutes. Fluoroscopy suggested that the contrast had entered venous channels.

Direct venous access can also occur during IM administration. Risk estimates for systemic toxicity reflecting inadvertent IV exposure were reported in 2 large datasets with IM penicillin G procaine and IM depot olanzapine. For penicillin G procaine, the risk for central nervous system procaine toxicity reflecting systemic exposure was 1 in 1308 injections (8 of 10,469 injections).(10) In the olanzapine depot drug development program, the risk for excessive sedation after IM injection reflecting systemic exposure was 1 in 1393 injections (25 events after 34,825 IM injections).(11) While these products do not contain castor oil or benzyl benzoate, the data suggest that direct venous access would be a potential risk for IM products that contain oil.

Lymphangiography involves injecting up to 14 mL of oil-based contrast media into a cannulated lymphatic in the lower extremities. The standard material used for this procedure is an iodinated ethyl ester of the fatty acids of poppy seed oil. Imaging of the lymphatic system is then performed after the injection. Appearance of the contrast material in the pulmonary vasculature has been documented with chest radiographs and chest computed tomography (CT) scans taken 24 hours after the injection. Bron et al demonstrated that contrast injected into dog lymphatic vessels entered adjacent veins through lymphatic-venous communications.(9) Thus, in this setting, inadvertent access of oil-based contrast occurs through lymphatic-venous communications.

Thus the radiocontrast and IM injection experience suggests plausible mechanisms for how oil-based products can inadvertently access the venous circulation and travel to the pulmonary vasculature. It is presumed that the presence of oil in the pulmonary vasculature precipitates cough. However, no mechanistic studies have documented the precise pathway by which the clinical effects occur.

Clinically, the most common presentation of POME is paroxysmal cough in close association with the injection. Cough begins either during or immediately following the injection but starting

no more than one hour after injection and lasts 5 to 10 minutes. AEs of cough in the immediate post-injection period have occurred in the AVEED development program and are consistent with this pattern of findings.

Cases of immediate post-injection cough have also been reported in the literature with other oil-based testosterone products not marketed in the US. In a study by Mackey et al, the tolerability of an IM testosterone enanthate formulation in a castor oil vehicle was assessed.(1) Over a period of 8 months, 26 men received a total of 551 injections. Sudden onset of non-productive cough associated with or without faintness occurred after 8 injections (1.5% of injections; 95% CI, 0.6%-2.9%). Coughing was transient, lasting for 10 minutes at most. None of the cases were considered serious or required medical intervention. All cases resolved spontaneously without sequelae.

In a second study of male contraception by Gu et al, the safety and efficacy of IM testosterone undecanoate in tea seed oil was assessed in 1045 men over a 30-month period.(2) Coughing after injection was reported in 22 patients. Approximately 24,094 injections were administered during the study for a post-injection cough rate of approximately 1 (95% CI, 0.5-1.3) per 1,000 injections.

These studies demonstrate that POME reactions can occur after IM injection of testosterone products. The prescribing information for an FDA approved IM depot-testosterone, Delatestryl® (testosterone enanthate in sesame oil), includes a precautions statement that “There have been rare postmarketing reports of transient reactions involving urge to cough, coughing fits, and respiratory distress immediately after the injection.”

Both castor oil and benzyl benzoate, the vehicle in AVEED, are used in other drugs and are listed in the FDA’s Inactive Ingredients Database. Preclinical data do not indicate that IM injection of castor oil and benzyl benzoate damage the lung.

A 13-week repeat dose toxicity study was conducted in male Sprague-Dawley rats where testosterone undecanoate (250 mg/mL) or placebo formulation (castor oil and benzyl benzoate) was injected biweekly (7 injections) at doses up to 1.6 mL/kg. The initial high dose was 3.2 mL/kg, but was reduced to 1.6 mL/kg following the second administration due to poor tolerability. The basis for the intolerability was unclear, but there was no evidence of respiratory effects or histologic findings in the lungs in animals that died early. There was also no evidence of pulmonary toxicity at the end of the treatment period based on the lack of histological changes in the lungs. The highest dose in this study (1.6 mL/kg) was 5.5-times the maximum human dose, based on mg/m<sup>2</sup> basis.

Even in the event the castor oil gains intravascular access, there is no evidence from animal testing that it causes toxicity based on available literature. IV administration of castor oil to anesthetized and spontaneously breathing intubated dogs was studied by Lorenz et al as part of an investigation of the tolerability of various solubilizing agents.(12) In these experiments, direct IV infusion of castor oil did not cause hives, edema, tachypnea, hypotension or deaths, nor did it cause significant histamine release. The dose of castor oil used in these studies is 3 times the human dose based on mg/m<sup>2</sup> basis, assuming intravasation of 100% of the intended IM injection.

### 7.1.2. Method to Characterize Post-Injection Reactions

Endo endeavored to characterize all post-injection reactions in both the TU clinical trial database and the spontaneous postmarketing safety database. Endo developed an adjudication process of case identification that would be transparent, objective and reproducible. In order to do this, 2 independent pulmonologists were engaged and asked to (a) develop a POME case definition; (b) using this definition, create a MedDRA terms-based screening search using PTs designed to retrieve all potential POME cases from all records in each dataset; and (c) review the potential cases for POME. From this work, a frequency of POME in the clinical trial database and a reporting rate in the spontaneous postmarketing database could be determined.

The 2 independent adjudicators have experience evaluating drug safety, in part through their prior employment at the FDA in the Division of Pulmonary and Allergy Drug Products. Dr. Marianne Mann is a former Deputy Director in the Division of Pulmonary and Allergy Drug Products and Dr. Robert Meyer is a former Office-level Director and Director in the Division of Pulmonary and Allergy Drug Products.

Because there are no published case definitions of POME, the adjudicators first reviewed the published literature on POME and then developed a case definition.

The independent adjudicator's case definition of POME is:

**Major criterion:** A paroxysmal cough in close association with the injection (during or immediately following injection classically, but starting no more than 1 hour after).

**Minor criteria:**

- Abnormal throat sensation (burning, tickling, fullness)
- Urge to cough
- Dyspnea
- Bronchospasm
- Diaphoresis
- Paresthesias of the circumoral region or hands/feet
- Bad taste in mouth
- Flushing, hot feeling (not defined as rash)

A POME case has the major and many minor criteria, however, if the major criterion is met and there are no signs of a true allergic event (eg, facial or periorbital edema), this is considered a POME case even if minor criteria are either absent or not described.

If there is no proximate cough, a case of dyspnea (without other explanatory reasons), bronchospasm and/or throat tickle/urge to cough can be a case IF proximate to injection (usually immediately, but no later than 1 hour) AND accompanied by at least 1 other minor criterion and allergic features do not support an allergic/immediate hypersensitivity reaction as the cause. If a pulmonary minor criterion is described alone with proximate timing, that case would be assessed as indeterminate. If a case has features consistent with POME, but clearly the majority of

features suggest the case is allergic in nature, this would not be considered a case since POME is not an allergic phenomenon.

POME has no patient specific risk factors, is thought to be related to injection technique and can occur with each injection. Therefore since the risk is considered as injection specific, the rates are reported as observed cases per 10,000 injections.

### **Non-POME Cases**

Events that definitively do not meet the definition for a POME case either in symptoms, signs and/or temporality (eg, a cough starting one week after treatment would NOT be considered a POME case)

### **Indeterminate Cases**

Cases were categorized as indeterminate if sufficient information or features to be put definitively into one of the above 2 categories were lacking: that is, a case that could not be determined to definitively be POME or to definitively be not POME. This would include cases described only as POME with no details as to symptoms or timing, or immediate hypersensitivity/anaphylaxis with no other details.

In addition to the case definition, they developed an AE coding-term based screening tool (a list of MedDRA PTs) to retrieve any potential cases of POME in the clinical and postmarketing safety databases. Initially they reviewed a list of preferred terms developed by Bayer, the maker of Nebido and other oil-based injectable formulations. This list, the Bayer MedDRA Query (BMQ) list of preferred terms, is used by Bayer to screen for POME cases for ongoing surveillance. The adjudicators could then add or remove PTs, using their experience, clinical judgment and information from literature descriptions of POME. The adjudicators selected over 500 MedDRA terms to identify potential cases of POME.

After the list of PTs was completed, the screening tool was employed to widely retrieve all potential cases of POME from the clinical and postmarket databases for further evaluation. The potential cases which contained the PTs were then reviewed by the adjudicators versus their case definition. They independently reviewed the potential cases with a review outcome of yes, no, or indeterminate. Their results were then compared and when they did not agree they discussed the case. If at the end of the discussion, they could not agree, then the most conservative interpretation was taken.

#### **7.1.3. Pulmonary Oil Microembolism Cases in Clinical Development**

The entire clinical trial database consisted of 3,556 subjects from both clinical and postmarketing trials. Using the broad group of search terms identified by the adjudicators, events occurring on the day of injection suggestive of POME were reviewed. One hundred two (102) subjects had 110 cases that occurred on the day of injection or had events missing the date of occurrence (Table 28).

Of the 102 subjects with 110 cases identified for further review, the adjudicators determined 3 cases of POME occurred in 3 subjects, 84 cases were non-POME cases and 23 cases in 22 subjects were indeterminate based on the adjudicators review versus their case definition.

Incidence rates for cases adjudicated as POME by dose and overall are shown in Table 28. Overall, the rate for cases adjudicated as POME was 1.5 cases (95% CI, 0-3.2) per 10,000 injections. A summary of each subject with an event adjudicated as POME or Indeterminate is shown in Table 40 and Table 41, respectively.

**Table 28: Risk Per Injection for Adjudicated Cases of Pulmonary Oil Microembolism in Clinical Development Database**

	<b>TU-750 mg (N=467)</b>	<b>TU-1000 mg (N=3089)</b>	<b>Overall (N=3556)</b>
Person-Years of Exposure	618.2	3603.7	4221.9
Number of Injections	3149	17068	20217
Number of cases retrieved by preferred terms suggestive of POME on day of injection	35 (34 subjects)	75 (68 subjects)	110 (102 subjects)
Number of cases Adjudicated as POME	0	3	3
Rate per 10,000 injections (95% CI)	0 (0, 11.7)	1.8 (0, 3.7)	1.5 (0, 3.2)
Rate per 10,000 patient-years <sup>a</sup> (95% CI)	0 (0, 59.5)	8.3 (0, 17.7)	7.1 (0, 15.1)
Rate per 10,000 patients <sup>a</sup> (95% CI)	0 (0, 78.7)	9.7 (0, 20.7)	8.4 (0, 18.0)

<sup>a</sup> Endo believes the rate per 10,000 injections is most appropriate where the risk is with each injection such as for these reactions. We have calculated alternate rates to allow comparisons when other denominators might be provided.

Note: Among subjects who received 1000 mg TU, the majority (n=2424, 78%) were enrolled in postmarketing studies. The design, objectives and conduct of these postmarketing studies were typical of non-interventional registries, and safety data collection in these studies was limited to suspected adverse reactions. The remaining subjects (n=665, 22%) were enrolled in clinical trials in which all adverse events were recorded irrespective of relationship to study drug.

The clinical characteristics of the POME events are similar to those reported in the literature for other oil-based products. All cases had symptoms of cough and/or dyspnea. Other symptoms such as dizziness, erythema, and hypotension were reported in some of the cases. The 23 cases that were adjudicated as indeterminate were reported as hyperhidrosis (8), hot flush or flush (5), dyspnea (3), cough (3), dysphonia (2), allergic respiratory disease (1), or hyperventilation (1) and are shown in Table 41. The cases of cough were adjudicated as indeterminate since onset relative to injection was not known. Note that 10 of the 23 cases were either reports of hyperhidrosis (8) or hot flush (2) observed in the male contraception studies. Because time of event was not recorded, it is not known if these events occurred before or after the injection of TU. Also, these symptoms could be confounded by the administration of a second hormonal agent since most subjects also received a progestational agent in these studies.

All indeterminate cases were considered to be clinically non-serious. One (1) case of POME was considered serious. The clinically serious case was severe cough that required medical observation but no medical intervention. Of the 3 subjects adjudicated to have had a POME event, 2 were subsequently re-treated with TU. Both subjects received 4 subsequent doses with no further reports of POME. Of the 23 subjects in which the adjudication was indeterminate,

9 were subsequently re-treated with TU without further events and 1 patient experienced POME on a subsequent injection.

With that said, it is important to realize that these events are generally self-limiting and do not require medical intervention. However, if they should occur, training and instruction under the REMS will ensure they are recognizable and manageable.

#### 7.1.4. Pulmonary Oil Microembolism Cases in Postmarketing Surveillance with Nebido

A systematic search and review for events was conducted in the Nebido postmarketing surveillance database using the same procedure as that for the cases in the clinical database. From the broad search, 547 cases were retrieved for adjudication by the independent pulmonologists. Utilizing the case definition the adjudicators developed, they determined 141 cases were POME cases, 324 cases were non-POME cases and 82 cases were indeterminate.

Concordance analysis was conducted to determine agreement between the 2 adjudicators using Fleiss' Kappa calculation for multi-category agreement (Table 29). A Kappa value of 1.000 (95% CI, 0.99-1.00) was determined indicating almost perfect agreement. A total of 81 indeterminate cases were agreed by both adjudicators; 1 indeterminate case was considered a "yes" by the other, so it is classified as "yes" in the final tabulation; 1 indeterminate case was considered as "no" by the other reviewer, so it is classified as "indeterminate."

**Table 29: Cross Table of the Assessment for Pulmonary Oil Microembolism Cases of the Two External Adjudicators (Postmarketing Surveillance)**

		Reviewer 2			Total
		Yes	No	Indeterminate	
Reviewer 1	Yes	140	0	0	140
	No	0	324	0	324
	Indeterminate	1	1	81	83
Total		141	325	81	547

Kappa 1.00 (95% CI, 0.99-1.00),  $p < 0.001$

Because these are post marketing surveillance data, a more conservative approach was taken in determining a reporting rate by adding cases classified as POME and those classified as Indeterminate for a total of 223 cases. Based on the number of doses sold (3,107,652), the POME reporting rate was 0.7 cases (95% CI, 0.6-0.8) per 10,000 doses sold.

Of the 223 cases adjudicated as POME, time of onset of symptoms was reported in 125 of cases (56%). In 124 cases (99%) with time reported, onset began within 30 minutes of injection. In 1 case onset was reported more than 30 minutes after injection. This patient experienced cough an hour after a Nebido injection. He stated that he "felt funny" when he went home but returned at an unspecified time and reported feeling better. His doctor considered this non-serious and prescribed antihistamines as treatment. For the remaining 98 cases, an onset time was not reported.

Of the 223 cases adjudicated as POME, 221 cases (99%) were reported as having resolved. Resolution was unknown for 2 cases (1%). No cases were reported as ongoing. A total of

92 cases (41%) resolved within 1 hour and 103 cases (46%) resolved but without a time reported. The time course of resolution is shown in Table 30.

A total of 13 cases (6%) received treatment with epinephrine. In 11 of the 13 instances where treatment with epinephrine was listed, the symptoms of POME started within 30 minutes of injection. Twenty-five (25) cases resulted in hospitalization, 6 of which were resolved in the emergency room. Of these 13 cases of POME, 6 were also adjudicated as yes for anaphylaxis, 2 as indeterminate, and 5 as no.

**Table 30: Time to Resolution of Cases Adjudicated as Pulmonary Oil Microembolism from Postmarketing Experience**

	<b>POME Cases</b>	<b>Indeterminate Cases</b>	<b>Combined Cases</b>
Number of Cases of POME	141	82	223
Summary of Resolution of Symptoms			
Resolved within 15 minutes	40 (28%)	15 (18%)	55 (25%)
Resolved within 15 to 60 minutes	32 (23%)	5 (6%)	37 (17%)
Resolved within 1 to 3 hours	7 (5%)	1 (1%)	8 (4%)
Resolved within 3 to 24 hours	12 (9%)	4 (5%)	16 (7%)
Resolved in more than 24 hours	2 (1%)	0	2 (1%)
Resolved with Time not reported	48 (34%)	55 (67%)	103 (46%)
Resolution Unknown	0	2 (2%)	2 (1%)

In conclusion, the potential for POME exists for oil-based drug products. In the AVEED clinical development program and in postmarketing surveillance experience, POME has been reported. However, these events occur immediately post injection at a low rate and typically resolve without intervention. No long-term sequelae or deaths have been reported. Most POME cases that have been reported with AVEED have not required medical intervention. However, because these events occur immediately post injection, they can be identified and managed by healthcare practitioners with an appropriate risk management plan.

## 7.2. Anaphylaxis

### 7.2.1. Background

Anaphylaxis is a rapid-onset, hypersensitivity syndrome which can affect multiple organ systems. An anaphylactic reaction is initiated when a foreign agent (eg, drug, food, insect venom) activates mast cells and basophils to release various vasoactive mediators, including histamine. IgE-mediated recognition of the agent is the classical mechanism by which the mast cells and basophils are activated. However, some agents, such as radio-contrast media, and opioids, directly activate mast cells and basophils and induce what has historically been referred to as an anaphylactoid reaction. Regardless of the mechanism of cell activation, the symptoms and severity of the reactions can be similar, and the reactions are now referred to collectively as anaphylaxis.

Warnings regarding the risk of anaphylaxis are in many if not most drug package inserts. What has been historically reported in the literature is medically significant anaphylaxis, which often manifests as anaphylactic shock. For instance, anaphylaxis to parenteral penicillin has been estimated to occur with an incidence of 0.3%, but severe reactions have an incidence of 0.01% to 0.05% with fatalities estimated to occur with an incidence of 0.001% to 0.002%.<sup>(13)</sup> This illustrates the challenge of estimating the risk of anaphylaxis, since both rate and severity need to be considered. The term anaphylaxis can be used to describe reactions which are primarily cutaneous and mild up to and including reactions which can be life-threatening. Delatestryl, depot testosterone enanthate, lists anaphylactoid reactions as a rare AE on its package insert, although there are no estimates of the incidence. Similarly, “anaphylactoid reactions” is listed as an adverse reaction on the package insert for testosterone cypionate, the other short-acting intramuscular testosterone product available in the US.

The symptomatology of anaphylaxis is variable, although typically the onset of symptoms is rapid after contact with the foreign agent. The onset varies between a few minutes to hours, partly depending on the route of exposure. For parenterals, such as AVEED, the onset is usually rapid.<sup>(14)</sup> The symptoms of anaphylaxis mainly involve the skin/subcutaneous tissue and mucosa, respiratory tract, cardiovascular system, and gastrointestinal system.

Although there is no consensus on the diagnostic criteria for anaphylaxis, one set of criteria was outlined at the 2006 Symposium on the Definition and Management of Anaphylaxis sponsored by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (Table 31),<sup>(7)</sup> and is commonly referred to by the senior author’s name, the Sampson criteria. The Sampson criteria were developed to provide the emergency responder or treating physician with a relatively simple and rapid means to make the diagnosis of anaphylaxis. In other words, the definition was designed primarily for day to day clinical use in a medical setting. The Sampson criteria are the FDA’s preferred criteria for evaluating anaphylaxis. These criteria when applied to clinical studies are sensitive, but less specific for anaphylaxis compared to expert review not using pre-set criteria.<sup>(15)</sup> Since the criteria do not factor in the intensity (severity) of the symptoms, cases with anaphylactic shock and cases with mild symptoms (eg, flushing and dyspnea) would both be captured through adjudication when applying the Sampson Criteria.

The Sampson criteria are divided into 3 levels (see Table 31), and the decision of which to apply is based on the likelihood that the patient is sensitive to the foreign agent (allergen). Criterion 1 is applied when it is not known or suspected that a patient is sensitive to an agent, criterion 2 is applied when it is *likely* that the patient is sensitive to the allergen, and criterion 3 is applied when the patient is known to be sensitive to the allergen. All 3 criteria require the acute onset of symptoms (minutes to hours) after exposure to the allergen.

Although anaphylaxis is a well described syndrome, and physicians and other HCPs are educated to the signs, symptoms and management, no cases of anaphylaxis were reported during clinical trials of AVEED. This would suggest that either the frequency of anaphylaxis was low enough that no cases were observed among the 3,556 patients treated, or that the cases were so mild that the symptoms were not recognized as anaphylaxis.

Cases consistent with anaphylaxis were noted in spontaneous postmarketing reports, so a retrospective post-hoc review and reanalysis of all cases from the clinical and postmarketing experience was performed.

**Table 31: Sampson Clinical Criteria for Diagnosing Anaphylaxis**

<p><b>Anaphylaxis is highly likely when any <u>one</u> of the following 3 criteria are fulfilled:</b></p> <ol style="list-style-type: none"> <li>1. <b>Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)</b>  <b>AND AT LEAST ONE OF THE FOLLOWING</b> <ol style="list-style-type: none"> <li>a. <b>Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)</b></li> <li>b. <b>Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)</b></li> </ol> </li> <li>2. Two or more of the following that occur rapidly after exposure to a <i>likely allergen for that patient</i> (minutes to several hours):           <ol style="list-style-type: none"> <li>a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)</li> <li>b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)</li> <li>c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)</li> <li>d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)</li> </ol> </li> <li>3. Reduced BP after exposure to <i>known allergen for that patient</i> (minutes to several hours):           <ol style="list-style-type: none"> <li>a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*</li> <li>b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline</li> </ol> </li> </ol>
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PEF=Peak expiratory flow; BP=Blood pressure

\* Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Excerpt from *J Allergy Clin Immunol.* 2006;117(2):393.(7)

### 7.2.2. Search Methodology

The two independent adjudicators, who reviewed the POME cases, also independently reviewed and categorized the clinical trial experience, as well as all cases reported in the Nebido postmarketing period, for anaphylaxis. There are well established search strategies to find potential cases of anaphylaxis. The independent adjudicators chose to use Standardized MedDRA Queries (SMQs) to retrieve potential cases of anaphylaxis. The potential cases were then reviewed versus the Sampson criteria to identify cases that met the criteria.

SMQs are groupings of MedDRA terms, ordinarily at the PT level that relate to a defined medical condition or area of interest. SMQs are intended to aid in the identification and retrieval of potentially relevant individual case safety reports. The SMQ project arose from the combined efforts of the MedDRA Shared Services Organization (MSSO) and an independent initiative by the Council for International Organizations of Medical Sciences (CIOMS); since May 2003, the joint results of the combined effort of the CIOMS Working Group and MSSO have been designated SMQs. The CIOMS Working Group is composed of senior scientists from several drug regulatory authorities, international pharmaceutical companies, the MSSO, the Japanese Maintenance Organization (JMO), the World Health Organization (WHO), and other institutions.

There are 2 SMQs that pertain to anaphylaxis, anaphylactic reaction and anaphylactic/anaphylactoid shock conditions. The 2 SMQs differ in focus. Anaphylactic/anaphylactoid shock (SMQ) is specific for more severe anaphylactic manifestations, ie, those that result in shock, and not less severe ones such as rash. Anaphylactic reaction (SMQ) widens the search beyond shock conditions by including PTs related to type I hypersensitivity reactions. To be comprehensive,

PTs from both SMQs, totaling 99 PTs were used to search for potential cases of anaphylaxis. These SMQs are designed as screening tools with broad scope, exhibiting high sensitivity and lower specificity. They retrieve every case containing even a single PT (eg, sign, symptom, physical finding, laboratory or other test data) that could be associated with anaphylaxis; therefore, many of the cases retrieved might not be expected to meet the Sampson criteria. The MedDRA guide indicates that after the broad search using the SMQs, a further review is required to identify actual cases.<sup>(16)</sup> Since the FDA requested that the Sampson criteria be applied, the screening with the SMQ broad search was followed by medical review by the independent adjudicators to identify cases that met the Sampson criteria.

Time of onset of symptoms is an important determinate in evaluating cases by the Sampson criteria. Because anaphylaxis has a rapid onset, particularly after parenteral exposure, the independent adjudicators chose to only evaluate cases from the clinical trial database which occurred on the day of injection. Time of onset of symptoms was also considered for cases in the spontaneous post-marketing database but was not used as a part of the automated search criteria.

Since men who had post-injection reactions to AVEED were not suspected to be sensitive to AVEED prior to the injection, the independent adjudicators chose to review the potential cases versus Sampson Criterion 1 (Table 31).

The independent adjudicators evaluated cases as yes, no, or indeterminate.

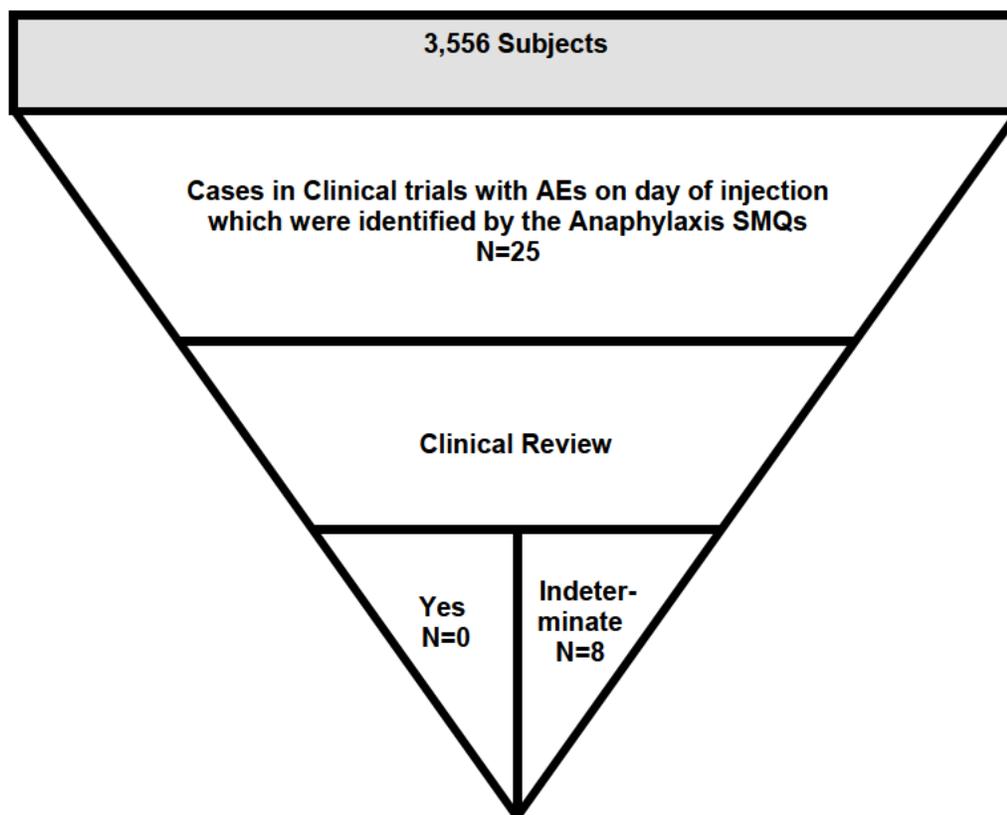
Once anaphylaxis has occurred in response to an agent, the patient is at risk for anaphylaxis upon future exposure to that agent. The risk therefore is considered patient specific, and therefore the rate are reported on a per patient basis.

### 7.2.3. Cases in Clinical Development

No cases of anaphylaxis were identified prospectively by the investigators during the course of the clinical studies. A retrospective review across the 3,556 subjects in the clinical development database, retrieved 25 cases (in 23 subjects) occurring on the day of injection based on the PT search. These cases underwent further review by the adjudicators (see Figure 7). Of these, none were adjudicated as “yes” based upon the Sampson criteria, and there were 8 cases (in 8 subjects) adjudicated as indeterminate (Figure 7). The rate of cases adjudicated as anaphylaxis is 0 cases (95% CI, 0-10.4)<sup>1</sup> per 10,000 patients (0 cases [95% CI, 0-8.7] per 10,000 patient-years).

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<sup>1</sup> The 95% CIs were calculated using normal approximation in general, but if a count is 0 its 95% CI was calculated using exact method based on binomial distribution.

**Figure 7: Anaphylaxis Screening Methodology for Clinical Cases**


Anaphylaxis is a systemic reaction, and thus a diagnosis based on the Sampson criteria requires symptoms in 2 different systems, except in a special case.<sup>1</sup> Since the subjects were not exposed to a likely allergen for that subject, the adjudicators evaluated the cases versus Sampson criterion 1 which requires both dermal/mucosal symptoms along with either cardiovascular or respiratory symptoms. Eight (8) cases (see [Table 32](#)) were adjudicated as indeterminate because the cases reported symptoms in only one body system (4 cases), had symptoms in 2 systems but neither was dermal/mucosal (3 cases) and had non-specific dermal symptoms (1 case). One (1) of the cases, which only had 1 system involved (“syncope”), was an SAE as described [below](#) (see also [Appendix 5](#)). None of the 8 cases adjudicated as indeterminate received any medical intervention (eg, epinephrine). Three (3) of the 8 cases were also adjudicated as indeterminate for POME.

Of the 8 subjects with cases adjudicated as indeterminate, 3 did not receive further TU treatment (2 discontinued and 1 had completed the course of treatment in the study). Two (2) subjects had 1 more injection after the episode adjudicated as indeterminate for anaphylaxis. Neither subject had episodes adjudicated as anaphylaxis but one of these subjects experienced dyspnea at the subsequent injection that was adjudicated as indeterminate for POME. The other subject had no

<sup>1</sup> The special case is when a patient with a *known* allergen sensitivity is re-exposed (see [Table 31](#)). This is not relevant here, since none of the patients had *known* sensitivities to AVEED, or any of its components.

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further post-injection reactions. One (1) subject had 5 subsequent injections and 1 subject had 6 subsequent injections, without further post-injection reactions. One (1) subject had 13 subsequent injections and, during the 10th subsequent injection experienced hyperventilation which was adjudicated to POME (indeterminate). The fact that 5 of the men tolerated re-challenge without anaphylaxis but only 2 cases adjudicated as indeterminate for POME, suggests that at least these 5 cases adjudicated as indeterminate for anaphylaxis were not true anaphylaxis. None of the cases were diagnosed as anaphylaxis by the study Principle Investigator.

Case 379-000024 (SAE) - This was a case report from a clinical trial describing a 50-year-old male who received Nebido between September 2003 and June 2006. In mid-June 2006, the patient was hospitalized for approximately 1 month for psycho-vegetative exhaustion with sleep disturbances. During that hospitalization he reported that he had had an episode of syncope during the month of March. In March 2006 he had received a dose of Nebido on March 14. At that time “cardiac causes could not be proven.” The temporal relationship between the syncopal episode and the injection of Nebido was not provided. No information about other symptoms that may have occurred with the syncopal episode or any treatment that might have been rendered was reported. The patient recovered from the event.

**Table 32: Listing of Cases Identified as Indeterminate for Anaphylaxis by the Independent Adjudicators**

Study No.	Subject No.	Treatment	Age/ Race	System Organ Class/Preferred Term(Verbatim Term)	TU Emergent	AE Onset Date/Time	AE Stop Date/Time	Previous TU Exposure Date/Time	SAE	Severity
306605	00379-000024	TU 1000 mg	50/ White	VASCULAR DISORDERS/ CIRCULATORY COLLAPSE (CIRCULATORY COLLAPSE AFTER PHYSICAL OVERLOAD)	Yes	Mar-2006	Mar-2006	2006-03-14/ 08:20	Yes	Moderate
97173	00001-000007	TU 1000 mg + Adjunctive	39/ White	VASCULAR DISORDERS/ CIRCULATORY COLLAPSE (COLLAPSE)	Yes	17-Sep-1998/ 17:25	17-Sep-1998/ 17:30	1998-09-17/ 17:35	No	Mild
	00001-000017	TU 1000 mg + Adjunctive	38/ White	VASCULAR DISORDERS/ CIRCULATORY COLLAPSE (COLLAPSE)	Yes	23-Dec-1998/ 12:37	23-Dec-1998/ 12:47	1998-12-23/ 12:35	No	Mild
AWB0105	00250-000002	TU 1000 mg	48/ Not Collected	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS/ OEDEMA (EDEMA, DIZZINESS, WEIGHT GAIN)	Yes	2-Sep-2005		2005-09-02	NC	Moderate
IP157-001B	00011-006089	TU 1000 mg	52/ White	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS/ DYSPNOEA (SHORTNESS OF BREATH)	Yes	30-Jan-2007	30-Jan-2007	2007-01-30/ 09:40	No	Mild
				SKIN AND SUBCUTANEOUS TISSUE DISORDERS/ ERYTHEMA (ERYTHEMA - NECK)	Yes	30-Jan-2007	30-Jan-2007	2007-01-30/ 09:40	No	Mild
IPASS	00059-005047	TU 1000 mg	54/ White	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS/ DYSPNOEA (INTERMITTENT BREATHLESSNESS)	Yes	20-Mar-2009		2009-03-20	No	Moderate
	00114-006161	TU 1000 mg	45/ White	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS/ COUGH (COUGH)	Yes	17-Dec-2007	17-Dec-2007	2007-12-17	No	Moderate
				VASCULAR DISORDERS/ HYPOTENSION (HYPOTENSION)	Yes	17-Dec-2007	17-Dec-2007	2007-12-17	No	Moderate
JPH04995	00001-000004	TU 1000 mg	49/ White	VASCULAR DISORDERS/ CIRCULATORY COLLAPSE (CIRCULATORY COLLAPSE)	Yes	15-Jul-1997/ 10:00	15-Jul-1997/ 10:10	1997-07-15/ 10:00	No	Severe

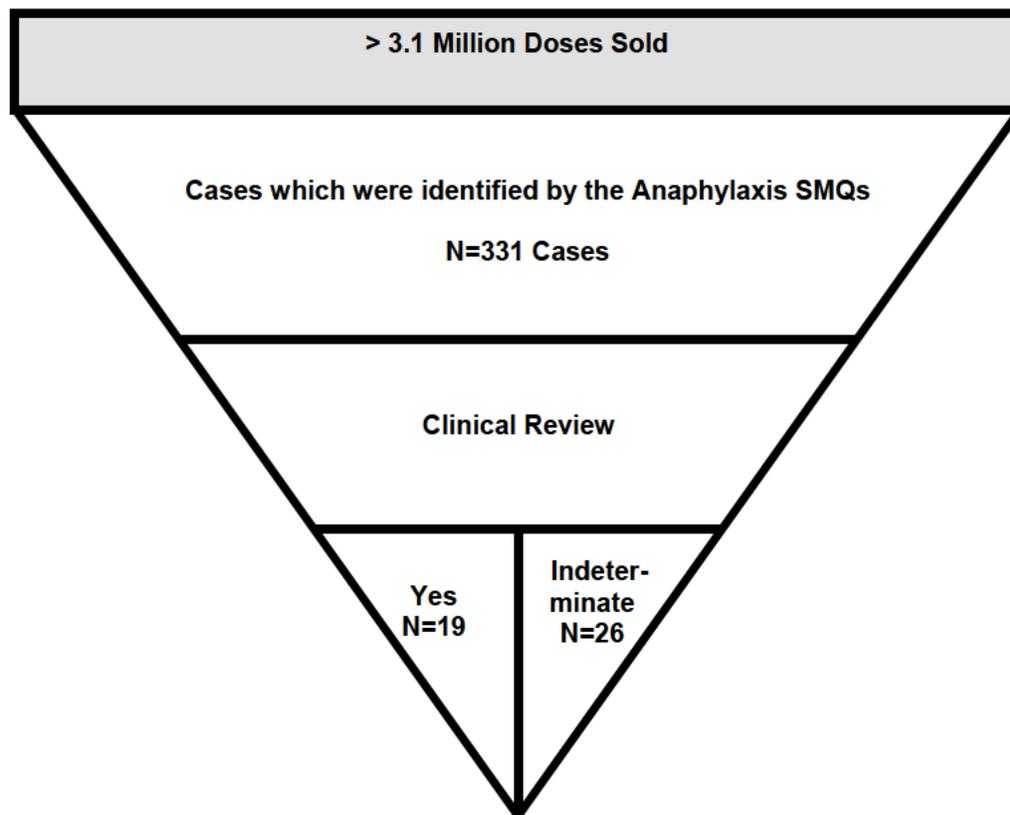
MedDRA version 14.0

AE=Adverse event; TU=Testosterone undecanoate, NC=Not collected

#### 7.2.4. Anaphylaxis Cases Reported in Postmarketing Experience

A systematic search and review for events was conducted in the Nebido postmarketing surveillance database using the same procedure as that for the cases in the clinical database. From the broad search, 331 cases were retrieved for adjudication by the independent adjudicators. Utilizing the Sampson case definition, they determined 19 were anaphylaxis cases, 286 cases were non-anaphylaxis cases and 26 cases were indeterminate (see Figure 8). Narratives of the 19 cases adjudicated as anaphylaxis are in [Appendix 3](#); narratives for the 26 cases adjudicated as indeterminate for anaphylaxis are provided in [Appendix 4](#).

**Figure 8: Anaphylaxis Screening Methodology for Postmarketing Reports**



Concordance analysis was conducted to determine agreement between the 2 adjudicators using Fleiss' Kappa calculation for multi-category agreement ([Table 33](#)). A Kappa value of 0.94 (95% CI, 0.90-0.99) was determined indicating excellent agreement. A total of 22 indeterminate cases were agreed by both adjudicators; 4 indeterminate cases were considered a “no” by the other, so to be conservative they were classified as “indeterminate” in the final tabulation thus making a total of 26 cases “indeterminate.” A total of 17 “yes” cases were agreed by both adjudicators; 2 cases were considered “yes” by one reviewer and “indeterminate” by the other, so to be conservative they were classified as “yes” in the final tabulation thus making a total of 19 cases “yes.”

**Table 33: Cross Table of the Assessment for Anaphylaxis Cases of the Two External Adjudicators (Postmarketing Surveillance)**

		Adjudicator 2			Total
		Yes	No	Indeterminate	
Adjudicator 1	Yes	17	0	0	17
	No	0	286	4	290
	Indeterminate	2	0	22	24
Total		19	286	26	331

Kappa 0.94 (95% CI, 0.90-0.99);  $p < .001$

Because postmarketing cases are spontaneous reports and some details may not be reported, Endo felt that a conservative approach to use with these spontaneous postmarketing cases was to combine cases adjudicated as yes and indeterminate for a total of 45 cases. The 45 cases were reported during a 9 year period during which time 3,107,652 doses of Nebido were sold. Based on an average persistence of 0.595 years, this means approximately 1,213,654 patients were treated with Nebido during this time. Therefore, the observed and reported anaphylaxis rate was 0.4 cases (95% CI, 0.3-0.5) per 10,000 patients (0.6 cases [95% CI, 0.4-0.8] per 10,000 patient-years).<sup>1</sup> The reporting rate of cases adjudicated as anaphylaxis (yes and indeterminate) has remained low and consistent since the launch of Nebido 9 years ago, [Table 39](#).

The onset of symptoms was reported for 31 (69%) of the 45 cases. All 31 cases with onset noted, had an onset of symptoms within 30 minutes. This is consistent with the Sampson criteria which notes that onset of symptoms are rapid (minutes to several hours). The 30-minute period is also consistent with the typical onset of allergic symptoms after subcutaneous immunotherapy (SCIT). A 30-minute wait is recommended in the guidelines for SCIT. SCIT, commonly known as allergen immunotherapy or desensitization, involves injecting graded doses of an allergen into a patient known to have a sensitivity to the allergen. The guidelines for SCIT are a relevant analog to an AVEED injection because in both situations a patient is injected with an allergen, (or a potential allergen in the case of AVEED), in which there is concern of an anaphylactic reaction. In the situation of AVEED, a patient who is potentially reactive to AVEED is injected with AVEED, while in SCIT a patient who is known to be reactive to an allergen is injected with the allergen. Thus, the 30-minute wait period post-injection is a reasonable precaution for men receiving AVEED.

The clinical characteristics of the 45 cases adjudicated as anaphylaxis suggest that most of the reactions were mild. There was no report of any therapy for 24 (53%) of the cases. Of the 21 (47%) treated cases, 8 received epinephrine (6 cases adjudicated as yes, 2 were adjudicated as indeterminate). The remaining 13 of the treated cases received antihistamines and/or steroids but

<sup>1</sup> The total number patients treated with Nebido was 1,213,654, which was estimated as the quotient of the total patient years (722,709.8) and the estimated median time on therapy (0.595 year, N = 284). Patient years were estimated from the 3,107,652 vials sold and an average dosing interval of 12 weeks, or 4.3 doses/year (52/12≈4.3) (722,709.8=3107652/4.3). Therefore, the estimated anaphylaxis rate was 0.37 (45\*10000/1213654; 95% CI, 0.26-0.48) per 10,000 patients.

did not receive epinephrine. Ten (10) of the cases were seen in an emergency room or were admitted to a hospital. There were no deaths reported from these anaphylactic reactions.

### **7.2.5. Rechallenge of Patients Adjudicated as Having Anaphylaxis**

AVEED is composed of three components, testosterone undecanoate, refined castor oil, and benzyl benzoate. Castor oil and benzyl benzoate are present in a number of other FDA approved drug products (Table 6). Makena, which contains both castor oil and benzyl benzoate, indicates on its package insert that products containing castor oil can cause allergic reactions including urticaria, pruritus and angioedema, although anaphylaxis is not specifically mentioned.

Skin testing is sometimes used to assess whether a patient is sensitive to a foreign agent, although there are limitations to this testing method including both false positive and false negative results. Skin testing has been performed on 3 patients who had post-injection reactions which were adjudicated as anaphylaxis. These skin tests were performed by the patients' physicians using reagents supplied by Bayer.

Case 1 - This patient (Case 200932012GPV) was a spontaneous case report was first received on September 14, 2009 from a physician (allergist) in Australia regarding a 16-year-old male patient with testicular agenesis who experienced an anaphylactic reaction less than three minutes after his third injection with Nebido (marketed as Reandron® in Australia). Symptoms included itching of his palms, groin and feet, followed by widespread/generalized urticaria, tightening in the throat, angioedema of the lips and face, shortness of breath, constriction of the chest, hypotension, cough and dizziness. He was treated with epinephrine, prednisolone, IV antihistamines and oxygen (by mask) by the general practitioner who administered the Reandron. The patient did not require airway intubation or ventilatory assistance, and there was no cardiopulmonary resuscitation given. The patient was taken to an Emergency Department but was not hospitalized overnight. The patient was referred to an allergist (the reporter). The allergist reported that the patient was an atopic individual (eczema, asthma, food allergies, other drug allergies). In addition, he reported that the patient was on no concomitant medications. A standard prick test was performed. One drop each of Reandron, Sustanon, Testogel, and Palini were applied (neat to skin) to the volar surface of forearm and pricked with lancet. The wheal size was 10×8 mm to Reandron after 10 and 15 minutes (no reaction to other reagents). Subsequently, the allergist tested the patient with the 3 ingredients of Reandron: castor oil, benzyl benzoate and TU. The patient had a strong positive reaction to benzyl benzoate. There was a large 10×10 mm wheal with a lot of peripheral smaller welts. The allergist stated that there was no doubt that it was the benzyl benzoate that the patient was reacting to. The independent adjudicators adjudicated this case as yes for anaphylaxis and indeterminate for POME.

Case 2 - This patient (Case 200828604GPV) is a 41-year-old male who had used Nebido for 6 years. He had a past medical history of Klinefelter's syndrome and hypertension. The patient experienced an anaphylactic reaction characterized by tightness in his chest, dry cough, burning eyes and flushing. He was treated with steroids and antihistamines and recovered after 30 minutes. One (1) month after the event he was given testosterone enanthate IM without adverse effect. Three (3) months later skin testing was negative for TU, castor oil, benzyl benzoate, saline, and latex, but positive for histamine. The independent adjudicators adjudicated this case as yes for POME and indeterminate for anaphylaxis.

Case 3 - This patient participated in study IP157-003, an Endo-sponsored study intended to re-challenge patients with suspicious post-injection reactions. This is the only patient who has agreed to participate in this study. The patient was a 38-year-old transsexual who in December 2004 developed hyperventilation, pronounced redness in the face, and hypertension (132/102 mm Hg) after his first dose of Nebido (Case DE-2004-037302). There were no urticaria noted but the patient complained of malaise and shivers. The patient was treated with IV prednisolone and oral antihistamines but was then discharged to home. In 2010 he participated in this double-blind, saline-controlled rechallenge protocol for patients who have experienced a potential anaphylactic reaction to Nebido (Case 201040508GPV). Skin prick tests to saline and the diluted Nebido, did not elicit a reaction nor did IM injections of diluted Nebido. However, after 0.4 mL of IM full-strength Nebido, the patient reacted after 15 minutes. It started with an erythema, most pronounced at face, breast, arms, and general feeling of warmth of the patient. In addition, blood pressure rose [value previous evening 140/90; before injection due to excitement 150/100; 30 minutes post-injection 205/130] and the patient had the fleeting feeling that there was a kind of external blockade in the thorax so that he could not breathe freely, although it was clarified by both auscultation and spirometry that there was no objective change in pulmonary function and especially that there was no airway obstruction. This reaction was therefore attributed to the high blood pressure and the skin sensations. The code was broken and it was determined that the patient had received Nebido. According to the protocol, the patient was treated with corticosteroids and antihistamines (prednisolone 250 mg IV, dimetinden (Fenistil) 2 mg IV, loratadine 10 mg orally). However, the reaction completely resolved within 20 minutes. The investigator, who is an immunologist, felt that this was neither allergic nor a pulmonary oily microembolism. The case was independently adjudicated as both a case of POME and a case of anaphylaxis.

Overall, of the 3 patients in the postmarketing experience who have had immediate post-injection AEs consistent with anaphylaxis, and had skin testing, 1 had a skin reaction to benzyl benzoate and the other 2 had no skin response to Nebido or its components.

In summary, similar to many parenterally administered drug products, anaphylaxis has been observed as a rare adverse drug reaction after the injection of TU. The majority of the cases adjudicated as anaphylaxis had mild symptoms and did not require treatment. No cases of anaphylaxis were identified prospectively by the investigators. In the entire postmarket experience, after >3.1 million dose have been sold, 45 cases have potentially matched the Sampson criteria for anaphylaxis. Of these 45, 21 were treated with epinephrine, steroids, or antihistamines. All patients recovered from the event and no patients died. As discussed below, our risk management plan is designed to mitigate risk by providing HCP and patient education, controlling conditions of drug administration and training in treating a reaction.

### **7.3. Overlap of Cases Adjudicated as POME and Anaphylaxis**

The diagnosis of either POME or anaphylaxis is based on clinical symptoms and signs without a “gold standard” objective test or assay. Both POME and anaphylaxis can present with similar symptoms, despite having underlying pathophysiologies which are likely very different. POME, a syndrome that many HCPs have not seen or learned about, often presents with symptoms including cough, urge to cough, dyspnea, bronchospasm, and flushing. Anaphylaxis, a syndrome on which most HCPs have been trained, can present with symptoms that overlap with POME

symptoms including respiratory symptoms (eg, cough, dyspnea, bronchospasm) and skin findings (eg, flushing). Consistent with these concepts, all the PTs used to identify potential anaphylaxis cases are included in the list of PTs used to identify potential POME cases.

Independent adjudication of post-injection reactions, to identify cases of POME and anaphylaxis, has been performed by experts in pulmonary medicine. Their adjudication for each diagnosis, based on clinical symptoms and signs, has been presented above. A comparison of the prospective criteria used to establish a case as POME or anaphylaxis makes clear that available clinical information may allow a case to be affirmatively adjudicated both, as POME and anaphylaxis, despite recognition that both pathophysiologies occurring concurrently after a single injection are extremely unlikely. Thus, the overlap of the results of the adjudication may help in better understanding the challenges in establishing a diagnosis and how this might impact how the cases were managed.

In the clinical trials, which included 3,556 subjects, the principal investigators did not identify any cases of anaphylaxis. The independent adjudicators also did not identify any cases as anaphylaxis, but identified 8 cases as indeterminate. Of these 8 cases, 3 were also adjudicated indeterminate for POME and 5 were not adjudicated as POME. None of these cases received any therapy for the AE, likely reflecting the judgment of the investigator present with respect to severity and/or the self-limiting nature of the event.

Because the postmarketing database is larger, the overlap in diagnosis of POME versus anaphylaxis is more apparent. Table 34 shows the adjudication of the postmarketing cases and the overlap that was identified. Of the 45 cases adjudicated as anaphylaxis (including the indeterminates), 43 (96%) were also adjudicated as POME. In contrast, of the 223 cases adjudicated as POME, only 43 (19%) were also adjudicated as anaphylaxis and 180 (81%) were not considered anaphylaxis. When the cases adjudicated as anaphylaxis (N=45) and POME (N=223) are considered separately, there are 268 cases, but when considered POME and anaphylaxis as a whole, because of the overlap there are actually only 225 unique cases.

**Table 34: Overlap in Independent Adjudication of Postmarketing Cases**

			POME (547 cases sent for adjudication)	
			Yes <sup>a</sup>	No
			223	324
<b>Anaphylaxis (331 cases)</b>	<b>Yes<sup>a</sup></b>	45	43	2
	<b>No</b>	286	164	122
<b>Not Adjudicated for Anaphylaxis</b>			16	200

<sup>a</sup> Yes is a combination of yes plus indeterminate.

There are several differences between the cases adjudicated as both POME and anaphylaxis and those only adjudicated as POME. The cases adjudicated only as POME are more likely to report cough with or without dyspnea (149/164, 91%) than cases adjudicated as both POME and anaphylaxis (25/43, 58%).

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Another not unexpected difference is the reporting of dermal findings of flushing in cases adjudicated as anaphylaxis. Sampson criterion 1 requires dermal findings for a positive adjudication. Of the 43 cases adjudicated as both anaphylaxis and POME, 12% (5/43) report flushing (dermal) while <1% (1/164) reported this finding in POME only cases. Flushing can be associated with vigorous coughing, so distinctions between POME and anaphylaxis based on this finding may be misleading.

In summary, there is overlap in the diagnostic features of the POME and anaphylaxis cases. When examined in aggregate because of the overlapping cases, the number of unique cases is smaller. Some of the POME cases may have also been considered anaphylaxis, because clinical findings, like flushing, which can occur with coughing may elevate a POME case to an anaphylaxis case.

## 8. PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS) AND ADDITIONAL RISK MANAGEMENT INTERVENTIONS

The proposed REMS and additional risk management interventions for AVEED have been designed with the assistance of a proactive, evidence-based risk assessment methodology to identify potential failures and underlying causes in the care delivery process for IM injections as targets for intervention. RxFMEA® is a proprietary software application (ParagonRx, Wilmington, DE) enabling users to achieve a systematic approach to REMS design while minimizing stakeholder burden. The process involves identifying the target risks, mapping the existing care delivery process, analyzing it for potential points where it may fail to protect the patients from risks, defining appropriate interventions for every significant hazard in the care process, and aggregating the intervention into feasible program elements. This methodology was used to assist and guide the development of the overall risk management program for AVEED in a way consistent with Endo's commitment to ensure patient safety. Endo will monitor and assess the components of the REMS and the additional risk management interventions on an ongoing basis to ensure that they are appropriate and achieving their purpose.

Immediate post-injection reactions with AVEED are infrequent, detectable, manageable, and generally self-limiting. The proposed REMS and additional risk management interventions are designed to:

- Educate HCPs and patients on the risks of AVEED
- Control the circumstances around the administration of the drug to enhance safety
- Allow identification and early intervention of post-injection reactions
- Reduce the likelihood of re-exposure for patients who have had a previous hypersensitivity reaction to AVEED or its components.

The RxFMEA, from which the proposed REMS and the additional risk management interventions were systematically designed, will ensure safe use of AVEED by mitigating failures in the care delivery process by:

- Communication of the risk of anaphylaxis and POME to HCPs and to patients by means of the Package Insert, Medication Guide and Dear HCP Letter
- Information warning against re-exposure after a suspected hypersensitivity reaction to AVEED or its components. This information will be provided in:
  - The Package Insert (Contraindication and Warning)
  - The Dear HCP Letter
  - The Medication Guide
- A 30-minute in-office waiting period to allow for early identification and management of post-injection reactions in a healthcare setting

- A controlled distribution system where AVEED is only shipped directly to HCPs, thus:
  - Facilitating administration in a healthcare setting and reducing the likelihood of patient self-administration
  - Allowing Endo to target prescribers of AVEED who did not previously receive the Communication Plan to receive it when ordering the drug
  - Reducing opportunities for diversion
- A video describing correct IM injection techniques to reduce the likelihood of intravascular administration
- Educational materials including a patient management algorithm to assist HCPs with proper recognition and management of symptoms of POME and anaphylaxis.
- Enhanced pharmacovigilance through passive and active surveillance of postmarketing adverse experience reports.

## 8.1. Risk Evaluation and Mitigation Strategy (REMS) Goals

The AVEED REMS will consist of a Communication Plan, Medication Guide, and REMS Assessments. The goals of the REMS are to ensure that:

- HCPs and patients understand the risks of an injection-based POME reaction and an anaphylactic reaction following the administration of AVEED.
- Patients remain at the healthcare facility or doctor's office for 30 minutes to allow early recognition and management of an injection-based POME reaction or an anaphylactic reaction following the administration of AVEED.

### 8.1.1. The 30-Minute Wait Time

The 30-minute wait time for the patient to remain at the HCP's office is to allow for early recognition and management of post-injection reactions following the administration of AVEED. The 30-minute period is consistent with the recommended 30-minute wait time for allergen immunotherapy (AIT) injections that is recommended by the American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI).<sup>(17)</sup> This is a worst-case scenario for experiencing post-injection anaphylaxis reactions since patients who are known to be reactive are injected with allergen. In AIT injections nearly all serious reactions begin within 30 minutes after allergen injection, which is therefore also an appropriate wait period for AVEED.

## 8.2. Communication Plan

The Communication Plan consists of a Dear HCP Letter that is intended to inform prescribers about the risks of an injection-based POME reaction or hypersensitivity reaction following the administration of AVEED. The content of the letter will include the importance of:

- Explaining the risks to patients

- Providing a Medication Guide to the patient with each injection
- The 30-minute in-office wait post-injection
- Not re-exposing patients who have had a previous hypersensitivity reaction to AVEED or its components
- Reporting AEs – especially an injection-based POME or hypersensitivity reaction – suspected to be associated with the administration of AVEED, and the various means of doing so

Endo will assure that the Dear HCP Letter, as an important part of the REMS, is made widely available. The Dear HCP Letter will be distributed within 45 days of the approval of AVEED and again within 45 days of the 6-month anniversary of the approval. Distribution will be targeted to likely prescribers of AVEED. As such, the letter will be sent to the membership of the following entities:

- The American Urological Association (AUA)
- The Endocrine Society
- The Sexual Medicine Society of North America (SMSNA)
- In addition, other primary care physicians, nurses, and physician assistants who are likely to prescribe or administer AVEED will receive the Communication Plan.

Endo will also disseminate the Dear HCP Letter by the following means:

- AVEED sales representatives will be trained on the goals of the AVEED REMS program and will distribute the Dear HCP Letter and a supply of Medication Guides on their first sales call to prospective or identified prescribers.
- On subsequent visits, sales representatives will provide a supply of Medication Guides.

A copy of the Package Insert and Medication Guide will be included with the Dear HCP Letter.

Ordering data for AVEED will be checked on a periodic basis to identify HCPs who did not previously receive the Dear HCP Letter and they will be sent the Dear HCP Letter.

Examination of postmarketing reports of post-injection reactions in conjunction with results from surveys of HCPs will help Endo to develop an understanding if the Communication Plan is a successful tool.

### **8.3. Medication Guide**

The purpose of the Medication Guide for AVEED is twofold:

- To provide patients important information about the risks of AVEED so they can make an informed decision on receiving the medication.
- To provide patients with important information about the need to wait in the office for 30 minutes after each injection and to report any post-injection reactions to their HCPs

Examples of the types of statements that would be included in the Medication Guide are shown here:

- Inform about the risk
  - AVEED may cause serious side effects.
  - This could cause you to cough, feel short of breath, feel dizzy, start to sweat, and have pain in your chest.
  - **You need to stay in the doctor's office, clinic, or hospital for 30 minutes after having the AVEED injection**
- Mitigate the effects of POME and anaphylaxis
  - **Tell your doctor or nurse or call 911** if you have any of these symptoms of a serious reaction after an AVEED injection. **You may need emergency treatment in a hospital.**
    - swelling of your face, tongue or throat
    - hoarseness, trouble breathing or speaking
    - feel flushed or dizzy
    - itching or rash
    - urge to cough

Results from surveys of patients will help Endo to develop an understanding if the Medication Guide is a successful tool

#### **8.4. Risk Evaluation and Mitigation Strategy (REMS) Assessments**

The REMS assessment plan will include a patient survey of the effectiveness of the REMS, including the Medication Guide, to help understand patients':

- Awareness and understanding of the risks of AVEED
- Awareness of the importance of remaining in the HCP's office for 30 minutes post-injection

HCPs will be surveyed to help understand the effectiveness of the REMS on HCP's awareness and understanding of the:

- Risks of AVEED
- Importance of the patient remaining in the HCP's office for 30 minutes post-injection

Based on the patient and HCP surveys, Endo will develop an understanding of:

- The level of compliance with the 30-minute waiting period
- Whether the patients received the Medication Guide and if so, the source (eg, HCP, internet)

- Whether the HCPs received the Communication Plan, and if so, the source (direct mailing, electronic mailing, internet, from sales representatives, etc)
- Assessments will be provided to the FDA at 12 months, 3 years, and 7 years.

## **8.5. Additional Risk Management Interventions**

In addition to the proposed REMS elements, Endo will implement additional risk management interventions related to the distribution of the drug, HCP and patient communications, and evaluation of the postmarketing AE experience.

### **8.5.1. Controlled Distribution System**

The controlled distribution system is an important component of our risk management interventions for AVEED and will ensure that AVEED will only be available through specialty pharmacies/distributors. The drug will only be shipped to a HCP for administration in a healthcare setting: it will not be available through retail pharmacies. This will reduce the likelihood of the drug being administered outside of a healthcare setting by ensuring that the therapy goes directly to the HCP who administers the injection. Furthermore, the 30-minute post-injection in-office patient wait can be enforced by the HCP to allow early recognition and treatment of post-injection reactions.

### **8.5.2. Additional Educational Materials and Other Tools**

The additional educational materials will consist of a video and instructional materials including a patient management algorithm that will be distributed with the Dear HCP Letter. They are designed to accomplish 3 objectives:

- To ensure that HCPs are knowledgeable about proper IM injection technique: slowly into the gluteus muscle after aspiration (to minimize the risk of accidental injection of the drug into the vasculature).
- To instruct in the types of post-injection reactions that might be encountered
- To help with recognition and early intervention if a post-injection reaction occurs.

The patient management algorithm will be distributed with the Dear HCP Letter and will provide specific advice to HCPs on how to recognize when a patient is having a post-injection reaction and how to manage the reaction. In particular, POME is not well known among HCPs in the United States because most IM injections are not oil-based and this phenomenon will not have been seen often during training and practice.

The patient management algorithm will:

- Provide a brief background on the of types of immediate post-injection reactions
- Assist with symptom recognition
- Provide advice on the treatment of symptoms (both initial and additional)
- Provide reference to peer-reviewed published Guidelines for additional information

A video will be made available via the website and via DVD that will reinforce the use of proper injection technique and that AVEED should be administered by slow, IM injection into the gluteal muscle with proper aspiration to ensure the tip of the needle is not in a blood vessel. This technique may reduce the accidental intravascular administration of the drug. The video will also remind HCPs to check that the patient has not previously experienced an allergic reaction to AVEED or its components. Further HCP and patient educational materials, including post-injection educational materials for patients, will be made available post-launch.

Endo will also make materials available and provide suggestions – via the sales force and through the product website – to assist HCPs in having patients remain in the office for the 30-minute wait. These will include reminder signage for around the office, a post-care instruction sheet that can be given to patients with the injection and departure times recorded, timers for those offices that would find this valuable, and educational materials for patients.

### **8.5.3. Enhanced Pharmacovigilance Activities**

Endo will utilize a dual approach to monitoring and evaluating postmarketing adverse events post-injection. For cases received spontaneously (traditional “passive” surveillance), Endo will utilize specialized collection forms to collect as much follow-up information as possible in a standardized fashion on all possible reports of injection-based POME reactions and anaphylactic reactions.

In addition, Endo will put into place an active surveillance program by partnering with groups that utilize EHRs. This will include EHRs utilized by urologists, who are likely to be early prescribers of AVEED, and EHRs more representative of primary care practices. By obtaining HIPAA-compliant data from these systems, Endo will be able to more accurately determine the rate of post-injection reactions in almost real-time because both the number of reactions and the number of injections administered will be known.

### **8.6. The European Union Safety Risk Management Plan (EU-SRMP) for Nebido**

The EU-SRMP for Nebido contains routine (defined as appropriate information in the product labeling) risk minimization measures for POME and anaphylaxis, and additional risk minimization activities for POME only ([Appendix 6](#)). The EU labeling for POME emphasizes that injections must be administered very slowly (over 2 minutes) and strictly intramuscularly, taking special care to avoid intravascular injection. The additional risk minimization activities for POME comprises delivery of educational activities at scientific conferences and making available written and audio-visual educational materials to prescribers and other HCPs. The emphasis on awareness, education and proper injection technique is consistent with the risk management plan that we have proposed for AVEED in the United States.

### **8.7. The AVEED Risk Evaluation and Mitigation Strategy (REMS) and Additional Risk Management Interventions – Summary**

The proposed AVEED REMS and additional risk management activities constitute a scientifically-designed and comprehensive plan that is designed to mitigate the known risks in the immediate post-injection period by:

- Ensuring HCPs are aware and knowledgeable about the risk of post-injection reactions
- Ensuring that AVEED injections are administered under the safest conditions possible
- Preparing HCPs to have their patients wait for 30 minutes post-injection and take appropriate action if a reaction occurs.
- Reducing the likelihood of a patient being re-exposed to AVEED if a previous hypersensitivity reaction occurred

All of these interventions will be monitored by appropriate REMS assessments and by passive and active surveillance of pharmacovigilance data. The diagram below summarizes this plan in reference to the time prior to injection, during injection, and during follow-up.

	<b>Prior to Access</b>	<b>At Time of Injection</b>	<b>Follow Up/ Confirmation</b>
HCP Letter	✓		
Medication Guide	✓		
<i>Administration video*</i>	✓	✓	
<i>Controlled distribution*</i>	✓		
30-minute wait		✓	✓
<i>Patient Management Algorithm*</i>	✓		✓
<i>30-min wait-adherence tools*</i>			✓
<i>Enhanced pharmacovigilance*</i>			✓
REMS Assessments			✓
* Additional (non-REMS) Risk Management Interventions			

## 9. BENEFIT/RISK DISCUSSION

Although, a number of TRT products are available, AVEED has unique benefits that provide another option for patients. One of the benefits of AVEED is its extended dosing interval which may contribute to the increased persistence observed and make it more favorable for patients to remain on therapy.

### 9.1. Testosterone Undecanoate-Benefits That Can Provide Another Option for Patients

Highlighted below are the benefits of AVEED therapy.

#### 9.1.1. Extended Dosing Interval

One of the key benefits of AVEED is continuous testosterone delivery over an extended period of time. The injection interval for AVEED, after the loading dose, is 10 weeks ( $\approx 5$  injections per year) compared with daily treatment for the topical therapies or 2 to 4 week intervals (13 to 26 injections per year) for the IM testosterone enanthate replacement therapy. Reducing dosing frequency may improve patient persistence to medication.

#### 9.1.2. Efficacious

AVEED is efficacious with 94.0% of subjects achieving normal testosterone blood levels, defined as  $C_{avg}$  300 to 1000 ng/dL, and only 5.1% of subjects with levels below the therapeutic range ( $C_{avg} < 300$  ng/dL). Other recently approved products also used the same criteria for approval. The percentage for topical formulations ranges from 77% to 87%. Other TRT products (short acting parenteral testosterone products and testosterone topical formulations) may require dose adjustment to achieve adequate serum testosterone levels.

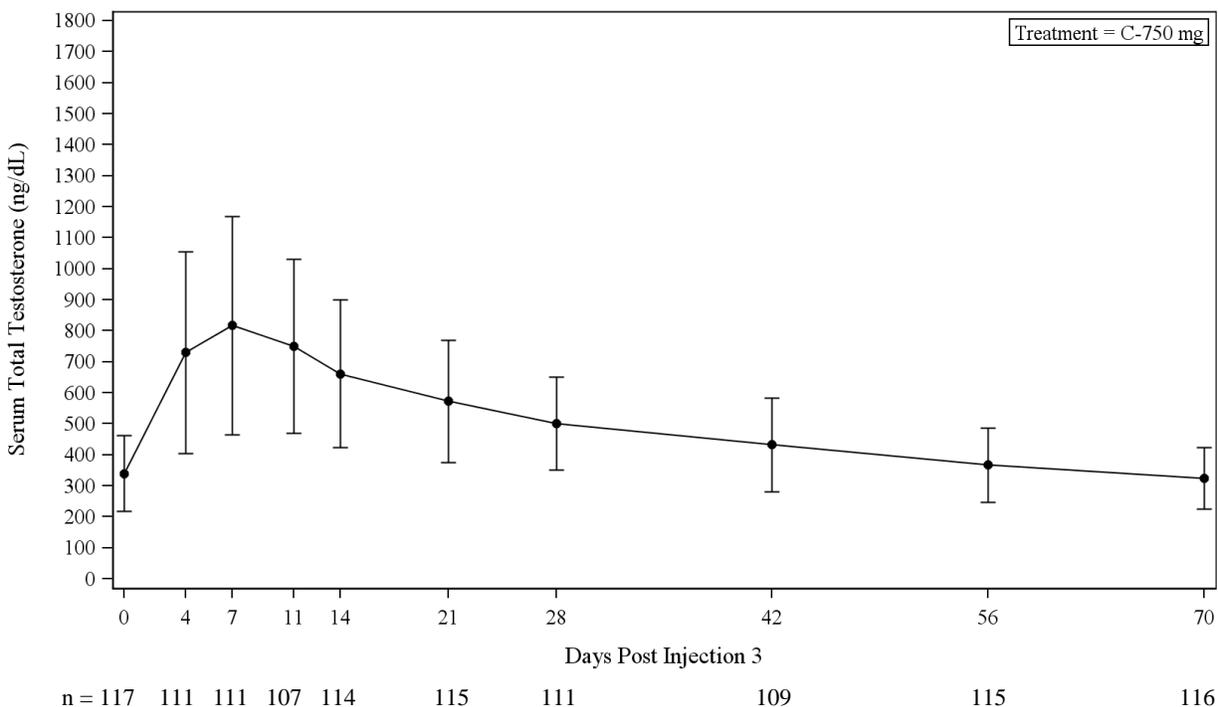
#### 9.1.3. No Risk of Transference

Unlike the transdermal gel formulations which are the most widely used products in the United States, there is no potential for unintended transfer of testosterone to women or children from men receiving AVEED. The secondary exposure, or transference, can cause virilization in women and children and irreversible changes in children (eg, fusion of bone plates), which led the FDA to require Black Box warnings about transference on all of these products. These products also require a Medication Guide as part of the REMS. Despite the change in labeling, the black box warning, and the REMS, there continue to be reports of AEs due to transference.

#### 9.1.4. Mean Testosterone Levels Do Not Exceed Supraphysiological Testosterone Levels

In the Phase 3 pivotal study (IP157-001 Part C and C2), treatment with AVEED 750 mg maintained mean testosterone concentrations in the eugonadal range over 10 week dosing interval (Figure 9). In contrast, for short acting injectable products, serum testosterone levels rise into the supraphysiological range, then decline gradually by the end of the dosing cycle (Figure 10).

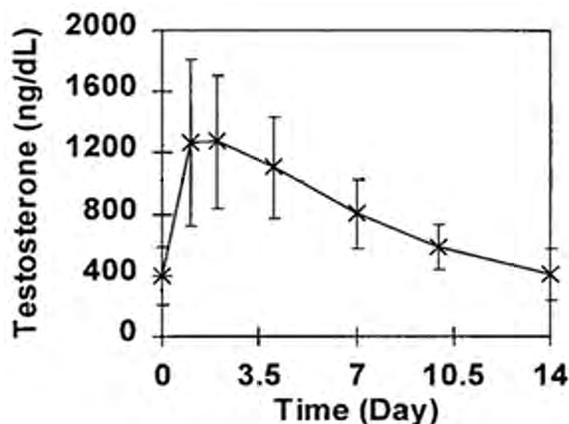
**Figure 9: Mean (SD) Serum Total Testosterone Concentrations (ng/dL) Resulting from the 3<sup>rd</sup> Intramuscular Injection of Testosterone Undecanoate**



Data Source: 5.3.5.1, Study IP157-001 Part C&D [Figure 14.2.1]

Note: C-750 mg refers to TU 750 mg.

**Figure 10: Steady-State Pharmacokinetic Profiles of Testosterone from Biweekly Intramuscular Injections of Testosterone Enanthate Measured at Week 16**



Data Source: *J Clin Endocrinol Metab.* 1999;84:3472.(6)

### 9.1.5. Extensive Safety Database

Safety data for AVEED are based on an extensive safety database of 18 completed clinical studies conducted in 3,556 subjects treated with TU. AE data from all parts of the US clinical study in hypogonadal men, European clinical studies in hypogonadal men, male contraception

studies in healthy subjects, and postmarketing studies in hypogonadal men provide supportive evidence of the safety of TU. Furthermore, the safety profile is supported by the extensive (>3 million ampules sold) and long-term (since 2003) marketed experience with Nebido (TU 1000 mg), which is the same formulation of TU, dosed at 4 mL (1000 mg) rather than 3 mL (750 mg). In the 9 years since Nebido was first introduced, it has never been withdrawn for any reason, (inclusive of safety reasons) in any of the 94 countries in which it is approved.

The general safety profile is similar to other TRT products particularly those administered by the IM route. Hypertension, prostatitis, increased PSA, acne, and sleep apnea syndrome are commonly reported with other TRTs and were seen in these trials.

## 9.2. Pulmonary Oil Microembolism and Anaphylaxis

The immediate post-injection reactions, POME and anaphylaxis, are AEs that occur rarely with AVEED/Nebido. Although any AE is of concern, these particular AEs have certain characteristics which lend themselves to mitigation through HCP and patient education and additional safe use measures. First, these AEs are rare (as defined below) and when they have occurred, there have been no reports of serious long-term sequelae. Second, they present mostly in the immediate post-injection period. Because of the proposed distribution and administration plan, the patient will be in the HCP's office during the immediate post-injection period, which allows for easy detection, monitoring, and, if necessary, management of the event. Lastly, the severity and nature of most of the events reported in clinical studies and in the postmarketing experience were such that they resolved spontaneously without requiring intervention.

Analysis of the TU exposure data from clinical and postmarketing studies in 3,556 subjects with more than 20,000 injections, indicate a low incidence of immediate post-injection reactions. Nebido has been marketed in more than 70 countries. Since approval in 2003 more than 3,100,000 doses have been sold. In spite of this large postmarketing experience, the number of reported cases of immediate post-injection reactions has been low, and the reporting rate has remained constant over time.

The rate of POME from clinical studies was 1.5 cases (95% CI, 0-3.2) per 10,000 injections. The reported rate of POME observed from the postmarketing database was 0.7 cases (95% CI, 0.6-0.8) per 10,000 doses sold.

No cases of anaphylaxis were identified by the investigator during the study. It was only by a retrospective review of AEs adjudicated using the Sampson criteria that these cases were identified. The rate of anaphylaxis from clinical studies was 0 cases (95% CI, 0-10.4) per 10,000 patients treated. The reported rate of anaphylaxis observed from the postmarketing database was 0.4 cases (95% CI, 0.3-0.5) per 10,000 patients.

Overall, the occurrence of POME and anaphylaxis is rare in the clinical trial experience and in the postmarketing environment, and there have been no reports of serious long-term sequelae from these reactions. No deaths have been reported due to these reactions.

Endo believes that the proposed REMS program, along with the additional risk management interventions and the product labeling, will effectively mitigate the identified risks of AVEED, including POME and anaphylaxis.

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The FDA-approved prescribing information will be an important element in the risk management plan for AVEED. The label will contain a detailed description of proper injection technique; dosing instructions; and a description of the immediate post-injection reactions to facilitate early recognition and management.

A Medication Guide reinforces information that HCPs will discuss with the patient before making the joint decision to begin or continue treatment. The Medication Guide will assure that patients understand whether they are suitable for treatment with AVEED, the risks of taking AVEED (in particular, immediate post-injection reactions of POME and anaphylaxis), the types of adverse signs and symptoms to report to the HCP, and the need to wait in the HCP's office for 30 minutes post-injection.

The REMS will include a Communication Plan for HCPs. The Communication Plan will include a Dear HCP letter informing prescribers about the medication risks and appropriate management of immediate post-injection reactions and a 30-minute wait in the office post-injection to allow for recognition and management of a post-injection event should it occur. Additional risk management interventions include a controlled distribution system, and educational materials for patients and HCPs, including a patient management algorithm and instructional video emphasizing proper injection techniques for HCPs.

Endo will conduct surveys of HCPs to measure their knowledge of, and compliance with, the risk minimization measures, and of patients to measure their knowledge and understanding of the key risk messages in the Medication Guide. The results of these assessments along with enhanced pharmacovigilance will be used to determine the effectiveness of the REMS, and whether changes to the REMS are necessary.

## 10. CONCLUSION

Hypogonadism is a condition that merits TRT. The Endocrine Society recommends replacement therapy for symptomatic men with androgen deficiency. Testosterone replacement can induce and maintain secondary sex characteristics, improve BMD, sexual function, sense of well-being, and muscle mass and strength.(3)

The goal of TRT is to achieve testosterone concentrations in the eugonadal range (300-1000 ng/dL) in order to treat the symptoms and prevent the complications of the deficiency.

All currently available forms of TRT have limitations and no one form is best for all men. The most popular forms of TRT – gels – must be applied daily leading to poor persistence, result in skin reactions, are associated with transference to women and children (for gels), and, in a proportion of men, result in inadequate testosterone replacement despite dose adjustment. Short-acting IM injections result in wide swings in blood testosterone levels after each injection and the need for relatively frequent administration (every 2 to 4 weeks).

Regardless of limitation, most patients discontinue therapy within several months. Persistence on therapy is important for clinicians to evaluate a response to treatment as well as for patients to achieve therapeutic benefit. The extended dosing interval of AVEED may contribute to the increased persistence observed and may make it be more favorable for patients to remain on therapy.

AVEED offers men with hypogonadism a new TRT formulation that achieves normal testosterone levels in most patients (94.0% of subjects in study IP157-001 Parts C and C2). AVEED does not carry the risk of transference, which may endanger children and women who inadvertently come into contact with men taking topical testosterone gel products. AVEED does not exceed supraphysiological testosterone levels like the short acting injectables. It does not require a surgical procedure like the pellets and does not result in gum irritation like the buccal preparation.

Like any pharmaceutical product, AVEED has its own profile of adverse reactions. Some of those reactions it shares in common with all TRTs but 2 are specifically related to the oily injection medium and are shared with the short-acting TRTs. These are POME and anaphylaxis. After review of an extensive safety database of 18 completed clinical studies conducted in 3,556 subjects treated with TU and over 3.1 million vials sold during a 9-year postmarketing experience, the frequency of both of these reactions can be described as rare.

Based on independently adjudicated results from the clinical database, POME occurs at a rate of 1.5 (95% CI, 0-3.2) cases per 10,000 injections. Similarly, based on independently adjudicated results from the clinical database, anaphylaxis occurs at a rate of 0 (95% CI, 0-10.4) cases per 10,000 patients treated. Endo has proposed a Risk Management Plan that makes prescribers and patients aware of these events, controls the circumstances around the time and place that injections are administered, and teaches prescribers how to respond should a reaction occur.

Based on the benefits and risks detailed in this briefing book, AVEED offers another option with unique characteristics for the patient and physician to consider.

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Endo believes that AVEED has a favorable benefit/risk ratio for men with hypogonadism who require TRT giving them an improved chance to stay on therapy. It offers unique benefits not available with other approved testosterone products and the large clinical development database and postmarketing experience around the world indicate that the identified serious risks are infrequent. Endo is confident that the proposed risk management plan – the product labeling and the REMS program, along with the additional risk management interventions (including a 30-minute in-office post-injection wait and a controlled distribution system) – will effectively mitigate the immediate post-injection risks associated with AVEED – POME and anaphylaxis. In conclusion, AVEED fulfills an unmet need in the United States.

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**APPENDIX 1. SUPPORTING TABLES AND LISTINGS**

Table 35	Summary of FDA-Approved Testosterone Replacement Therapies
Table 36	List of Clinical and Postmarketing Studies Included in the Summary of Clinical Safety
Table 37	A Comparison of Similar Adverse Events Across Products with AVEED
Table 38	Cases of Pulmonary Oil Microembolism (Potential and Identified by Independent Adjudicators as Yes or Indeterminate) by Time of Initial Case Report
Table 39	Cases of Anaphylaxis (Potential and Identified by Independent Adjudicators as Yes or Indeterminate) by Time of Initial Case Report
Table 40	Listing of Cases of Pulmonary Oil Microembolism Identified Through Independent Adjudicators – Subjects Treated with Testosterone Undecanoate
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**Table 35: Summary of FDA-Approved Testosterone Replacement Therapies**

Formulation	Regimen	Pharmacokinetic Profile (Percent of Patients Achieving Normal Levels of Testosterone)	Highlights of Product Characteristics (See Labels for Full Details)
Topical Formulations			
Testim (testosterone gel 1%) • Original approval 2002	50 or 100 mg T qd	• $C_{avg}$ within normal range in 74% of patients on Day 90	• Black box warning regarding secondary exposure • In a 90-day controlled trial - Application site reactions occurred in 2%-4% of patients
AndroGel (testosterone gel 1%) • Original approval 2000	50, 75, or 100 mg T qd	• $C_{avg}$ within normal range in 87.0% of patients on Day 180	• Black box warning regarding secondary exposure • In a 180-day clinical trial - Application site reactions occurred in 3%-5% of patients
AXIRON (testosterone topical solution 2%) • Original approval 2010	30-120 mg T qd	• $C_{avg}$ within normal range in 84.1% of patients on Day 120	• Black box warning regarding secondary exposure • In a 120-day clinical trial - Application site reactions occurred in 7% of patients • Solution applied to axilla
FORTESTA (testosterone gel 2%) • Original approval 2010	10-70 mg T qd	• $C_{avg}$ within normal range in 77.5% of patients on Day 90 • $C_{max}$ 1800-2499 ng/dL in 1.6% of patients on Day 90; no patients with $C_{max} \geq 2500$ ng/dL	• Black box warning regarding secondary exposure • In a 90-day clinical trial - Application site reactions occurred in 16.1% of patients
AndroGel 1.62% (testosterone gel 1.62%) • Original approval 2011	20.25 – 81 mg T qd	• $C_{avg}$ within normal range in 81.6 % of patients on Day 112 • $C_{max}$ 1800-2499 ng/dL in 5.5% of patients on Day 112; 2 patients with $C_{max} \geq 2500$ ng/dL	• Black box warning regarding secondary exposure • In a 182-day clinical trial - Application site reactions occurred in 0.9% of patients

**Table 35: Summary of FDA-Approved Testosterone Replacement Therapies (Continued)**

Formulation	Regimen	Pharmacokinetic Profile (Percent of Patients Achieving Normal Levels of Testosterone)	Highlights of Product Characteristics (See Labels for Full Details)
Transdermal System			
Androderm (patch) <ul style="list-style-type: none"> <li>Original approval 1995</li> </ul>	2.0 mg or 4.0 mg/day	<ul style="list-style-type: none"> <li><math>C_{avg}</math> within normal range in 97% of patients treated on Day 28</li> </ul>	<ul style="list-style-type: none"> <li>In a 182-day clinical trial               <ul style="list-style-type: none"> <li>Application Site reactions include:                   <ul style="list-style-type: none"> <li>Application Site Pruritus 17%</li> <li>Application Site Vesicles 6%</li> </ul> </li> </ul> </li> </ul>
Injectable Formulations			
Testosterone enanthate injection <ul style="list-style-type: none"> <li>Original approval 1953</li> </ul>	50-400 mg Q2-4 weeks IM	<ul style="list-style-type: none"> <li>In a study of IM injections of testosterone enanthate 200 mg injected every 2 weeks in 33 hypogonadal men, steady-state PK profiles of the sex hormones were evaluated over a 14-day interval, starting at week 16. Testosterone enanthate produced fluctuation in T levels between the supraphysiological and low-normal range. Mean serum concentrations for T increased sharply after IM injection to levels at or above the ULN. These values then decreased gradually into the normal range over the 14-day dosing interval. Peak serum T concentrations (mean <math>C_{max}</math>) averaged <math>1462 \pm 408</math> ng/dL and occurred <math>2.3 \pm 1.9</math> days after injection</li> </ul>	<ul style="list-style-type: none"> <li>Intramuscular administration include:               <ul style="list-style-type: none"> <li>Rare postmarketing reports of transient reactions involving urge to cough, coughing fits, and respiratory distress immediately after the injection</li> </ul> </li> <li>Adverse Reactions include:               <ul style="list-style-type: none"> <li>Rarely, anaphylactoid reactions</li> <li>Inflammation and pain at injection site</li> </ul> </li> </ul>

**Table 35: Summary of FDA-Approved Testosterone Replacement Therapies (Continued)**

Formulation	Regimen	Pharmacokinetic Profile (Percent of Patients Achieving Normal Levels of Testosterone)	Highlights of Product Characteristics (See Labels for Full Details)
<p>Testosterone cypionate injection</p> <ul style="list-style-type: none"> <li>Original approval 1979</li> </ul>	<p>50-400 mg every 2-4 weeks IM</p>	<ul style="list-style-type: none"> <li>Following IM administration in an oily vehicle, testosterone ester is slowly absorbed into the general circulation and then rapidly hydrolyzed in plasma to testosterone.</li> <li>In a randomized crossover study of 6 healthy males aged 20-29 years, the PK of a single injection of 200 mg testosterone cypionate was compared to that of a single injection of 194 mg testosterone enanthate. Mean serum testosterone concentrations increased sharply to 3 times the basal levels (approximately 1350 ng/dL) at 24 hours and declined gradually to basal levels (approximately 500 ng/dL) by Day 10.</li> <li>A similar observation was noted in a clinical study of replacement therapy with a single IM dose of 200 mg testosterone cypionate in 11 hypogonadal males aged 28-74 years.</li> <li>PK analysis showed a 3-fold mean increase in serum testosterone concentrations by Day 2 (<math>1108 \pm 440</math> ng/dL) and a progressive decline to basal serum levels (<math>360 \pm 166</math> ng/dL) by Day 14 for the group. These PK studies demonstrated the dosing regimen of 200 mg testosterone cypionate every 2 weeks led to initial elevation of serum testosterone into the supraphysiological range and then a gradual decline into the hypogonadal range by the end of the dosing interval.</li> </ul>	<ul style="list-style-type: none"> <li>Adverse Reactions include : <ul style="list-style-type: none"> <li>Hypersensitivity including skin manifestations and anaphylactoid reactions</li> <li>Inflammation and pain at the site of IM injection</li> </ul> </li> </ul>

**Table 35: Summary of FDA-Approved Testosterone Replacement Therapies (Continued)**

Formulation	Regimen	Pharmacokinetic Profile (Percent of Patients Achieving Normal Levels of Testosterone)	Highlights of Product Characteristics (See Labels for Full Details)
Buccal System			
Striant (buccal, bioadhesive, testosterone tablets) <ul style="list-style-type: none"> <li>Original approval 2003</li> </ul>	30 mg controlled-release, bioadhesive tablets bid	<ul style="list-style-type: none"> <li>C<sub>avg</sub> within normal range in 76% of patients treated at Week 12</li> <li>C<sub>avg</sub> within normal range in 84% of patients treated on Day 7</li> </ul>	<ul style="list-style-type: none"> <li>In a 12-week clinical trial application site reaction include :               <ul style="list-style-type: none"> <li>Gum or mouth irritation 9.2%</li> <li>Taste bitter 4.1%</li> <li>Gum pain 3.1%</li> <li>Gum tenderness 3.1%</li> <li>Gum edema 2.0%</li> </ul> </li> </ul>
Pellets for Implantation			
Testosterone pellets <ul style="list-style-type: none"> <li>Original approval 1972</li> </ul>	3-6 pellets implanted SC	<ul style="list-style-type: none"> <li>Serum T peaks at 1 month and then is sustained in normal range for 3-6 months, depending on formulation</li> </ul>	<ul style="list-style-type: none"> <li>Adverse Reactions include:               <ul style="list-style-type: none"> <li>Anaphylactoid reactions (rarely)</li> <li>Inflammation and pain at injection site</li> <li>Extrusion of pellets</li> </ul> </li> </ul>

bid=Twice a day; C<sub>avg</sub>=Average concentration; C<sub>max</sub>=Maximum concentration; IM=Intramuscular; PK=Pharmacokinetics; Q=Every; qd=Every day; SC=Subcutaneous; T=Testosterone; ULN=Upper limits of normal

**Table 36: List of Clinical and Postmarketing Studies Included in the Summary of Clinical Safety**

Study Number/ Status	Indication	Title	Type	Study Design	Treatments
<b>US Clinical Study</b>					
<b>IP157-001</b> Completed	Hypogonadism	A 2-arm, open-label, randomized, multicenter pharmacokinetic and long-term safety study of intramuscular (IM) injections of testosterone undecanoate (TU) 750 mg and 1000 mg in hypogonadal men  This is a 5-part protocol that includes 2 IM treatment arms in Part A, 2 IM treatment arms in Part B, a single IM treatment arm in Part C, a single IM treatment arm in Part C2, and 2 subcutaneous (SC) treatment arms in Part D.	Phase III	Randomized, 2-arm, active-controlled, multiple-dose	<b>Part A:</b> TU 750 mg IM TU 1000 mg IM <b>Part B:</b> All subjects received TU 1000 mg IM initial dose followed by two arms of: TU 750 mg IM TU 1000 mg IM <b>Part C:</b> TU 750 mg IM <b>Part C2:</b> TU 750 mg IM <b>Part D:</b> TU 1000 mg SC (Part A subjects) TU 750 mg SC (Part C subjects)
<b>European Clinical Studies</b>					
<b>JPH01495</b> Completed	Hypogonadism	Study to investigate the pharmacokinetics of TU after single IM injection	Phase I	Open-label, single-arm, single-dose	TU 1000 mg IM
<b>JPH04995</b> (includes LTFU study) Completed	Hypogonadism	Study to investigate the pharmacokinetics and efficacy of TU after multiple IM injections in hypogonadal men	Phase II/III	Open-label, single-arm, multiple-dose	TU 1000 mg IM

**Table 36: List of Clinical and Postmarketing Studies Included in the Summary of Clinical Safety (Continued)**

Study Number/ Status	Indication	Title	Type	Study Design	Treatments
<b>ME98096</b> (includes 2 LTFU studies) Completed	Hypogonadism	Open-label study to evaluate safety and pharmacokinetic parameters of total and free testosterone after repeated IM administrations of TU 1000 mg (5 injections over 36 weeks) in hypogonadal male subjects	Phase II	Open-label, single-arm, multiple-dose	TU 1000 mg IM
<b>ME97029</b> (includes 2 LTFU studies) Completed	Hypogonadism	Study to investigate the efficacy and safety of TU vs. testosterone enanthate (TE) after IM injection in hypogonadal men	Phase III	Randomized, open-label, parallel-group, 2-arm, active-controlled, multiple-dose	TU 1000 mg IM TE 250 mg IM
<b>306605</b> (includes LTFU study) Completed	Hypogonadism	Open-label, 1-arm study to investigate safety and efficacy of IM injections of TU 1000 mg in hypogonadal men at variable intervals during a 136-week to 192-week treatment including pharmacokinetics of TU during steady state in a subgroup of 30 subjects  Long-term safety and efficacy of IM injections of TU including pharmacokinetics during steady state	Phase III	Open-label, single-arm, multiple-dose	TU 1000 mg IM
<b>303934</b> Terminated Early <sup>a</sup>	Male andropause	A monocenter, prospective, randomized, double-blind, parallel-group, placebo-controlled, long-term clinical trial to investigate the effects of a long-acting IM preparation of TU on andropause-related symptoms	Phase II	Randomized, double-blind, parallel-group, 2-arm, placebo-controlled, multiple-dose	TU 1000 mg IM Placebo 4 mL IM

**Table 36: List of Clinical and Postmarketing Studies Included in the Summary of Clinical Safety (Continued)**

Study Number/ Status	Indication	Title	Type	Study Design	Treatments
<b>European Male Contraception Studies</b>					
<b>97028</b> Completed	Male contraception in healthy males	Male contraception with TU vs. combined administration of TU and levonorgestrel (LNG) - a double-blind, randomized, single-center comparative study	Phase II	Randomized, double-blind, parallel-group, 2-arm, placebo-controlled, multiple-dose	TU 1000 mg IM + oral placebo TU 1000 mg IM + oral LNG
<b>97173</b> Completed	Male contraception in healthy males	Male contraception with a sequential regimen of cyproterone acetate (CPA) and TU followed by a lower dose of CPA and TU in normal men	Phase II	Randomized, single-blind, 3-arm, placebo-controlled, multiple-dose	<b>Induction Phase:</b> All subjects received TU 1000 mg IM + CPA 20 mg/day oral <b>Maintenance Phase:</b> Randomized to 1 of the following 3 regimens: TU 1000 mg IM + CPA 20 mg/day oral TU 1000 mg IM + CPA 2 mg/day oral TU 1000 mg IM + daily oral placebo
<b>98016</b> Completed	Male contraception in healthy males	A single-center, prospective, 1-arm, uncontrolled study to investigate the efficacy and safety of male contraception with TU and norethisterone enanthate (NET-EN) over 24 weeks	Phase II	Open-label, single-arm, multiple-dose	TU 1000 mg IM + NET-EN 200 mg IM
<b>99015</b> Completed	Male contraception in healthy males	Study on efficacy and safety of male contraception with TU and NET combined in different application regimens	Phase II	Randomized, open-label, parallel-group, 3-arm, active-controlled, multiple-dose	TU 1000 mg IM + NET-EN 200 mg IM TU 1000 mg IM + NET-EN 400 mg IM TU 1000 mg IM + NET-A 10 mg/day oral

**Table 36: List of Clinical and Postmarketing Studies Included in the Summary of Clinical Safety (Continued)**

Study Number/ Status	Indication	Title	Type	Study Design	Treatments
<b>42306</b> Completed	Male contraception in healthy males	A phase IIb, double blind, placebo- controlled, randomized, multicenter, multiple dose trial investigating the efficacy, safety and pharmacokinetics of a subcutaneous etonogestrel (ENG) rod combined with IM TU for male fertility control	Phase IIb	Randomized, double-blind, parallel-group, 7-arm, placebo- controlled, multiple-dose	TU 750 mg IM + Low Release ENG Implant every 10 weeks TU 750 mg IM + Low Release ENG Implant every 12 weeks TU 1000 mg IM + Low Release ENG Implant every 12 weeks TU 750 mg IM + High Release ENG Implant every 10 weeks TU 750 mg IM + High Release ENG Implant every 12 weeks TU 1000 mg IM + High Release ENG Implant every 12 weeks Placebo IM + Placebo Implant
<b>Postmarketing Studies</b>					
<b>AWB 0105</b> Completed	Androgen deficiency	Efficacy and tolerability of Nebido®	Post- marketing surveillance: prospective, non- interventional	Open-label, single-arm, multiple-dose	TU 1000 mg IM
<b>39732</b> <b>(NE0601</b> <b>IPASS)</b> Completed	Hypogonadism	International, multicenter post authorization surveillance study on the use of Nebido® to assess tolerability and treatment outcomes in daily clinical practice (IPASS Nebido®)	Post- marketing surveillance: non- interventional observational	Open-label, single-arm, multiple-dose	TU 1000 mg IM
<b>14329</b> <b>(Czech NEO)</b> Completed	Hypogonadism	NEO; Observational post-marketing study (NEbido)	Post- marketing surveillance: Non- interventional observational	Open-label, single-arm, multiple-dose	TU 1000 mg IM

**Table 36: List of Clinical and Postmarketing Studies Included in the Summary of Clinical Safety (Continued)**

Study Number/ Status	Indication	Title	Type	Study Design	Treatments
<b>NB02</b> Completed	Hypogonadism	NEBIDO Therapy in Hypogonadal Male Patients With Paraplegia With Osteoporosis Compared With Conventional Osteoporosis	Post-marketing surveillance: Non-interventional observational	Open-label, 3-arm, multiple-dose, single center	TU 1000 mg
<b>TG09</b> Completed	Hypogonadism	Efficacy and tolerability of Testogel/Nebido in combination with a standardized exercise and diet programme in hypogonadal male patients with abdominal obesity compared with exercise and diet programme	Post-marketing surveillance: Non-interventional observational	Open-label, 2-arm, multiple-dose, single center	TU 1000 mg, Testogel
<b>14853</b> Terminated Early <sup>b</sup>	Hypogonadism	Effect of exercise alone or in combination with testosterone replacement on muscle strength and quality of life in older men with low testosterone concentrations; a randomized double-blind, placebo controlled study	Post-marketing surveillance: Interventional	Randomized, Double blind, parallel-group, 2-arm, placebo controlled, multiple-dose	TU 1000 mg, Placebo

Data Source: Data Integration Plan for EN3331 Integrated Summary of Safety (dated 30-May-2012) (5.3.5.3, AVEED ISS [Appendix E]).

<sup>a</sup> Terminated early by Sponsor

<sup>b</sup> Terminated early due to slow recruitment rate.

CPA=Cyproterone acetate; ENG=Etonogestrel; IM=Intramuscular; LNG=Levonorgestrel; LTFU=Long-term follow up; NET-A=Norethisterone acetate; NET-EN=Norethisterone enanthate; SC=Subcutaneous; TE=Testosterone enanthate; TU=Testosterone undecanoate.

**Table 37: A Comparison of Similar Adverse Events Across Products with AVEED**

<b>Treatment-Emergent Adverse Events</b>	<b>AndroGel 1.62% vs Placebo Study Duration 182 days N=234</b>	<b>Axiron Study Duration 120 days N=155</b>	<b>AVEED Study Duration 182 days N=725</b>
PSA increased	26 (11.1%) <sup>a</sup>	2 (1.0%)	10 (1.4%)
Hypertension	5 (2.1%)		11 (1.5%)
Hematocrit	5 (2.1%)	6 (4.0%)	2 (0.3%)
Hyperlipidemia	≤ 2%		3 (0.4%)

<sup>a</sup> Prostate-specific antigen (PSA) values that met pre-specified criteria for abnormal PSA values as well as those reported as adverse events.

**Table 38: Cases of Pulmonary Oil Microembolism (Potential and Identified by Independent Adjudicators as Yes or Indeterminate) by Time of Initial Case Report**

	11/25/03-11/24/07	11/25/07-11/24/08	11/25/08-11/24/09	11/25/09-11/21/10	11/22/10-11/24/11	Total Over All Time Periods
Number of Potential Cases	143	75	120	89	116	543
Number of Cases Identified by Clinical Review (Yes or Indeterminate)	49	26	48	43	57	223
Number of Doses Sold	614586	466419	587474	671668	767505	3107652
Rate of Cases of POME Identified by Clinical Review per 10,000 Doses Sold	0.80	0.56	0.82	0.64	0.74	0.72

Note: Potential cases of POME are identified through a broad MedDRA preferred term search. Cases of POME are identified by Independent Adjudicators out of the potential cases of POME. Time periods are based on the PSUR designated time periods.

Program: i\_arate.sas; Output: i\_arate.rtf; Date: 19-Feb-2013

**Table 39: Cases of Anaphylaxis (Potential and Identified by Independent Adjudicators as Yes or Indeterminate) by Time of Initial Case Report**

	11/25/03-11/24/07	11/25/07-11/24/08	11/25/08-11/24/09	11/25/09-11/21/10	11/22/10-11/24/11	Total Over All Time Periods
Number of Potential Cases	78	39	76	59	78	330
Number of Cases Identified as Yes or Indeterminate	9	7	7	10	12	45
Number of Ampoules Sold	614586	466419	587474	671668	767505	3107652
Number of Treatment Years	142927.0	108469.5	136621.9	156201.9	178489.5	722709.8
Rate of Cases of Anaphylaxis Identified as Yes or Indeterminate per 10,000 Ampoules Sold	0.146	0.150	0.119	0.149	0.156	0.145
Rate of Cases of Anaphylaxis Identified as Yes or Indeterminate per 10,000 Treatment Years	0.630	0.645	0.512	0.640	0.672	0.623

Potential cases of Anaphylaxis are identified through a broad MedDRA preferred term search. Cases of Anaphylaxis are identified by Independent Adjudicators out of the potential cases of Anaphylaxis. Time periods are based on the PSUR designated time periods

Program: i\_arate\_ext.sas; Output: i\_arate\_ext.rtf; Date: 28-Feb-2013

**Table 40: Listing of Cases of Pulmonary Oil Microembolism Identified Through Independent Adjudicators – Subjects Treated with Testosterone Undecanoate**

Study No.	Subject No.	Treatment	Age/ Race	System Organ Class/Preferred Term (Verbatim Term)	TU Emergent	AE Onset Date/Time	AE Stop Date/Time	Previous TU Exposure Date/Time	SAE	Severity
306605	02115-000184	TU 1000 mg	52/ White	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS/ COUGH (COUGH AFTER INJECTION)	Yes	2006-04-03/ 09:01	2006-04-03/ 09:15	2006-04-03/ 09:00	Yes	Mild
IPASS	00004-017019	TU 1000 mg	44/ White	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS/ COUGH (COUGH ON INJECTION FOR THE FIRST TIME)	Yes	2010-05-15	2010-05-15	2010-05-15	No	Mild
	00158-036010	TU 1000 mg	60/ Asian	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS/ IMMEDIATE POST-INJECTION REACTION (FLUSHING, SENSATION OF WARMTH, SWEATING, ORO-PHARYNGEAL DISCOMFORT, HEARTBURN IMMEDIATELY AFTER INJECTION)	Yes	2007-08-29	2007-08-29	2007-08-29	No	Mild

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AE=Adverse event; SAE=Serious adverse event; TU=Testosterone undecanoate

**Table 41: Listing of Cases of Indeterminate Pulmonary Oil Microembolism Identified Through Independent Adjudicators – Subjects Treated with Testosterone Undecanoate**

Study No.	Subject No.	Treatment	Age/ Race	System Organ Class/Preferred Term (Verbatim Term)	TU Emergent	AE Onset Date/Time	AE Stop Date/Time	Previous TU Exposure Date/Time	SAE	Severity
306605	01559-000001	TU 1000 mg	60/ White	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS/ DYSPHONIA (HOARSENESS)	Yes	2003-05		2003-05-28/ 08:25	No	Mild
	01617-000099	TU 1000 mg	54/ White	VASCULAR DISORDERS/ HOT FLUSH (HOT FLUSH)	Yes	2003-11-03		2003-11-03/ 11:00	No	Moderate
	02115-000184	TU 1000 mg	52/ White	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS/ DYSPNOEA (DYSPNEA AFTER INJECTION)	Yes	2006-04-03/ 09:01	2006-04-03/ 09:15	2006-04-03/ 09:00	Yes	Mild
42306	00010-105020	TU 750 mg + Adjunctive	42/ White	SKIN AND SUBCUTANEOUS TISSUE DISORDERS/ HYPERHIDROSIS (SEVERE EXCESSIVE SWEATING)	Yes	2004	2004-08-16	2004-10-21/ 15:20	No	Severe
	00038-106010	TU 750 mg + Adjunctive	29/ White	SKIN AND SUBCUTANEOUS TISSUE DISORDERS/ HYPERHIDROSIS (SWEATING MORE AT TIMES (POST IMPLANT))	Yes	2004-07		2004-07-21/ 13:05	No	Mild
	00072-114002	TU 750 mg + Adjunctive	34/ White	SKIN AND SUBCUTANEOUS TISSUE DISORDERS/ HYPERHIDROSIS (INCREASED SWEATING)	Yes	2004-02-02	2004-10-15	2004-02-02/ 11:40	No	Moderate
	00080-113017	TU 1000 mg + Adjunctive	29/ White	VASCULAR DISORDERS/ HOT FLUSH (HOT FLUSHES)	Yes	2004-04-02	2004-05-13	2004-04-02/ 13:23	No	Moderate
	00080-113022	TU 1000 mg + Adjunctive	39/ White	VASCULAR DISORDERS/ HOT FLUSH (HOT FLUSHES)	Yes	2004-04-23	2004-08-28	2004-04-23/ 09:20	No	Mild
97028	00001-000001	TU 1000 mg + Adjunctive	37/ White	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS/ ALLERGIC RESPIRATORY DISEASE (ALLERGIC RESPIRATORY DISEASE)	Yes	1997-10-10	1997-11-10	1997-10-10/ 16:35	No	Mild
99015	00001-000003	TU 1000 mg + Adjunctive	26/ White	SKIN AND SUBCUTANEOUS TISSUE DISORDERS/ HYPERHIDROSIS (SWEATING)	Yes		2000-01-23	1999-09-20/ 06:53	No	Mild
	00001-000018	TU 1000 mg + Adjunctive	24/ White	SKIN AND SUBCUTANEOUS TISSUE DISORDERS/ HYPERHIDROSIS (INCREASED SWEATING)	Yes		Ongoing	1999-10-18/ 08:35	No	Moderate

**Table 41: Listing of Cases of Indeterminate Pulmonary Oil Microembolism Identified Through Independent Adjudicators – Subjects Treated with Testosterone Undecanoate (Continued)**

Study No.	Subject No.	Treatment	Age/ Race	System Organ Class/Preferred Term (Verbatim Term)	TU Emergent	AE Onset Date/Time	AE Stop Date/Time	Previous TU Exposure Date/Time	SAE	Severity
	00001-000026	TU 1000 mg + Adjunctive	25/ White	SKIN AND SUBCUTANEOUS TISSUE DISORDERS/ HYPERHIDROSIS (SWEATING)	Yes		1999-12-13	1999-10-19/ 09:10	No	Severe
	00001-000029	TU 1000 mg + Adjunctive	30/ White	SKIN AND SUBCUTANEOUS TISSUE DISORDERS/ HYPERHIDROSIS (SWEATING)	Yes		Ongoing	1999-11-03/ 09:30	No	Moderate
				SKIN AND SUBCUTANEOUS TISSUE DISORDERS/ HYPERHIDROSIS (SWEATING)	Yes		2000-05-01	1999-11-03/ 09:30	No	Moderate
	00001-000031	TU 1000 mg + Adjunctive	24/ White	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS/ COUGH (COUGH)	Yes		2000-04-03	1999-10-19/ 09:50	No	Severe
	00001-000038	TU 1000 mg + Adjunctive	37/ White	SKIN AND SUBCUTANEOUS TISSUE DISORDERS/ HYPERHIDROSIS (SWEATING)	Yes		Ongoing	1999-11-19/ 07:19	No	Mild
				SKIN AND SUBCUTANEOUS TISSUE DISORDERS/ HYPERHIDROSIS (SWEATING)	Yes		2000-04-01	1999-11-19/ 07:19	No	Mild
AWB0105	00055-000002	TU 1000 mg	39/ NC	VASCULAR DISORDERS/ HOT FLUSH (HOT FLUSHES)	Yes	2005-05-12		2005-05-12	NC	Severe
IP157-001A	00037-004129	TU 750 mg	43/ White	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS/ DYSPHONIA (HOARSENESS)	Yes	2006-06-14	2006-06-15	2006-06-14/ 09:00	No	Mild
IP157-001B	00011-006089	TU 1000 mg	52/ White	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS/ DYSPNOEA (SHORTNESS OF BREATH)	Yes	2007-01-30	2007-01-30	2007-01-30/ 09:40	No	Mild
				RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS/ DYSPNOEA (INTERMITTENT SHORTNESS OF BREATH)	Yes	2007-04-02	2007-04-16	2007-04-02/ 09:50	No	Mild
IP157-001C	00050-007006	TU 750 mg	53/ White	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS/ COUGH (COUGH)	Yes	2007-07-12	2007-07-12	2007-07-12/ 08:10	No	Mild
IPASS	00020-064062	TU 1000 mg	71/ White	VASCULAR DISORDERS/ FLUSHING (FACIAL FLUSHING)	Yes	2009-05-13	2009-12-10	2009-05-13	No	Moderate
	00059-005047	TU 1000 mg	54/ White	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS/ DYSPNOEA (INTERMITTENT BREATHLESSNESS)	Yes	2009-03-20		2009-03-20	No	Moderate

**Table 41: Listing of Cases of Indeterminate Pulmonary Oil Microembolism Identified Through Independent Adjudicators – Subjects Treated with Testosterone Undecanoate (Continued)**

Study No.	Subject No.	Treatment	Age/ Race	System Organ Class/Preferred Term (Verbatim Term)	TU Emergent	AE Onset Date/Time	AE Stop Date/Time	Previous TU Exposure Date/Time	SAE	Severity
	00114-006161	TU 1000 mg	45/ White	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS/ COUGH (COUGH)	Yes	2007-12-17	2007-12-17	2007-12-17	No	Moderate
JPH04995	00001-000004	TU 1000 mg	49/ White	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS/ HYPERVENTILATION (HYPERVENTILATION)	Yes	1999-06-09	1999-06-09	1999-06-09/ 10:20	No	Moderate

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AE=Adverse event; NC=Not collected; SAE=Serious adverse event; TU=Testosterone undecanoate

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## APPENDIX 2. DEATHS DURING THE TESTOSTERONE UNDECANOATE CLINICAL DEVELOPMENT PROGRAM

Study Number	Subject Number	Adverse Event Resulting in Death (Verbatim Term)
306605	01615-000067	Pneumonia
IP157-001A	00070-004006	Stab Wounds
IP157-001A	00078-004162	Massive Stroke
IP157-001B	00001-006020	Malignant Neoplasm of Lung
IP157-001C	00078-007012	Fatal Myocardial Infarction
IP157-001C	00050-007010	Cardiac Arrest
IPASS	00103-002051	Suicide, Cause Unknown
ME97029	00001-000012	Traffic Accident; pat. was riding a motor cycle, lost power over the cycle and collided with a truck
NB02	00001-000039	Multiple Organ Failure Fatal Staphylococcus Aureus Sepsis [LLT: Staphylococcus Aureus Septicaemia]

**Subject 01615-000067/Study 306605**

<b>Patient (Set)</b>	Patient number: 67 (b) (6)		<b>Study site / Investigator:</b> Study center 6 / Dr. C. Boehme	
<b>Demographic data (Screening)</b>	Age: 58 years			Race: Caucasian
	Weight: 98 kg	Height: 183 cm		BMI: 29.3 kg/m <sup>2</sup>
<b>Start</b>	Start of treatment (SOT): 17 Jul 2003			
<b>Nature and timing of SAE</b>	Investigator's term: 1) Aggravation of thrombocytopenia (Morbus Werlhof or Werlhof's disease); 2) Pneumonia <sup>54</sup> ; 3) Sepsis		HARTS term: 1) Thrombocytopenia; 2) Pneumonia; 3) Sepsis	
			MedDRA preferred term: 1) Thrombocytopenia; 2) Pneumonia; 3) Sepsis	
	CIOMS No.: DE-2005-004831 <i>Event verbatim:</i> Pneumonia with lobe abscess <sup>54</sup> [Lobar pneumonia] ([Respiratory failure], [Pneumonia legionella], [Lung abscess]); Sepsis [Sepsis] ([Legionella infection]); Aggravation of thrombocytopenia (Werlhof's disease) [Idiopathic thrombocytopenic purpura] ([Condition aggravated], [Thrombocytopenic purpura], [Petechiae])			
	Date of SAE: 1) 11 Feb 2005; 2)+3) 07 Mar 2005		Time after SOT: 1) 576 days; 2)+3) 600 days	
End of SAE: -		Outcome: 1) Not recovered; 2) Fatal (b) (6); 3) Not recovered		

(Continued)

<sup>54</sup> Initial investigator's term read "Pneumonia with lobe abscess". For coding reasons, the term was split in Pneumonia (SAE) and Lobe abscess (AE). The investigator accepted this solution and completed a data correction form.

**SAE description**

The following conditions were known from the medical history of the patient: lower lobe resection due to tuberculosis in 1979, benign scrotal surgery in 1986, arthrodesis of L5/S1 in 1998, and pancreatitis due to choledocholithiasis in 1999 and cholecystectomy in 2001. Concurrent medical conditions included thrombocytopenia, hypertension, overweight (BMI = 29.26 kg/m<sup>2</sup>), osteoporosis, and mild glaucoma. Concomitant medications included calcium for osteoporosis, hydrochlorothiazide, valsartan (Co-Diovan) for hypertension, fentanyl (Durogesic) for back pain, and timolol for glaucoma.

In spite of low levels of thrombocytes seen at screening, the patient was included in the study under the condition to be closely monitored regarding the condition of thrombocytopenia. During the study treatment with TU (9 TU injections), thrombocyte levels ranged from 82 to 111 Gpt/L (Normal range: 150 – 450 Gpt/L).

On (b) (6) the patient was hospitalized due to prednisolone refractory thrombocytopenia with thrombocyte levels of 8 to 10 Gpt/L. The following examinations were performed: ECG, upper abdominal and renal ultrasound, gastroscopy and subsequent histology, as well as bone marrow cytology and histology (bone marrow examination showed unspecific reactive myelopathy). Due to inefficacy of high-dose prednisolone therapy, therapy with azathioprin (Imurek) for immunosuppression was introduced on (b) (6) on. On (b) (6) the patient complained about exertional dyspnea. A chest X-ray revealed right lower lobe infiltration. Antibiotic treatment was started: ceftriaxon (Rocephin) and fluconazole (Diflucan). The microbiology test indicated Legionnaire's pneumonia. On (b) (6) the patient was transferred to a specialized university hospital (Oncology ward (b) (6) (b) (6) Due to increasing respiratory insufficiency, he was transferred to the Internal medicine ward [Cardiology, angiology, pulmonology, intensive care] on (b) (6).

With a history of idiopathic thrombopenic purpura, platelet counts worsened probably secondary to pneumonia. The treatment was changed from steroids and initial antibiotic treatment (Ceftriaxon / Fluconazol) to Imipenem / Cilastatin plus Vancomycin because of increasing inflammation parameters and worsened respiratory situation. In spite of thrombocytes replacement, the patient presented with haemoptyses, when platelets showed values of 70 Gpt/L. Elective intubation and bronchoscopy were performed (mild diffuse mucosal bleeding). The patient developed a marked septic shock with high need of catecholamines. X-ray showed cloudiness of the right lung and increasing infiltrations left. The circulatory and respiratory situation deteriorated in spite of assisted ventilation, also temporary renal failure occurred. Cardiac arrest was treated with resuscitation limited to mechanic measures because of infaust prognosis and multi-organ failure. The patient died on (b) (6).

The autopsy report confirmed sepsis, lobe-covering partly abscess-forming pneumonia, and thrombocytopenia (Werlhof's disease).

**Characteristics of SAE**

<b>Intensity</b>	1), 2), 3) Severe	<b>Drug treatment</b>	Yes
<b>Main pattern</b>	Continuous	<b>Non-drug treatment</b>	Yes
<b>Study drug action</b>	Dose not changed	<b>Outcome</b>	1) Not recovered; 2) Fatal; 3) Not recovered

**Assessment of drug relationship of SAE**

<b>- by the investigator</b>	Causality as reported: 1), 2), 3) None
<b>- by the sponsor</b>	Causality as determined: <b>Unlikely</b> for pneumonia with lung abscess and for sepsis; <b>None</b> for aggravation of thrombocytopenia (Werlhof's disease)

**Subject 00070-004006/Study IP157-001A**

Patient ID	Study Number	Site Number	Treatment	
070-4006	IP157-001 Part A	070	750 mg testosterone undecanoate (TU) 5 injections given intramuscular (IM) at 12-week intervals	
Age	Race	Sex	Last Treatment Date	
54	Caucasian	Male	11-Aug-2006	
Past Medical History				
Secondary hypogonadism (2006), headaches secondary to motor vehicle accident (2001), kidney stones (2004), excised tumor on his left cheek (2004), hypercholesterolemia (2001), and neck pain 2001)				
Adverse Event		Stab Wounds		
Onset Date	Severity	Relationship	Outcome	
21-Oct-2006	Severe	Definitely not related	Death	
Narrative				
<p>A 54-year-old Caucasian male (070-4006) was enrolled in Study IP157-001 Part A, a 2-arm, open-label, randomized multicenter pharmacokinetic and long-term safety study of IM injections of 750 mg or 1000 mg TU in hypogonadal men. The patient was enrolled in the 750 mg dosing arm and received the 1st injection of study drug on 19-May-2006 and Injection 2 on 11-Aug-2006.</p> <p>On [REDACTED] (b) (6), following a 2nd injection of study drug on 11-Aug-2006, patient experienced an attack and stabbing by his son-in-law. The patient's wife reported that the patient was stabbed 45 times while trying to break up a physical altercation between his daughter and his son-in-law.</p> <p>Event was deemed severe, definitely not related to study drug, and the outcome was death. The SAE term and cause of death was stabbing. No autopsy was performed.</p> <p>The patient had received 2 injections of the study drug prior to this event.</p> <p>Concomitant medications taken at time of event included: Paxil CR, Lipitor, TRICOR, and hydrocodone.</p> <p>The Investigator assessed the relationship between event and study drug as definitely not related, and the Medical Monitor agreed with the Investigator's assessment.</p>				

**Subject 00078-004162/Study IP157-001A**

Patient ID	Study Number	Site Number	Treatment	
078-4162	IP157-001 Part A	078	1000 mg testosterone undecanoate (TU) injections given intramuscular (IM) at 12-week intervals	
Age	Race	Sex	Last Treatment Date	
68	Caucasian	Male	29-Jan-2008	
Past Medical History				
COPD(1996), hypertension (1974), coronary artery disease (1992) with triple bypass (2003), edema (2003), left bundle branch block (1992), colon polyps (2005) with removal (2006), erectile dysfunction (2003), benign prostatic hypertrophy (1995), arthritis (2006), general body aches (1995), bilateral abdominal hernias (1993), with repair (1998), itchy scalp (2001), athlete's foot (2003), hyperlipidemia (1993), tonsillectomy (1999), seasonal allergies (2004), and secondary hypogonadism (2003)				
Adverse Event		Massive Stroke		
Onset Date	Severity	Relationship	Outcome	
10-Apr-2008	Severe	Definitely not related	Death	
Narrative				
<p>A 68-year-old Caucasian male (078-4162) was enrolled in Study IP157-001 Part A, a 2-arm, open-label, randomized multicenter pharmacokinetic and long-term safety study of IM injections of 750 mg or 1000 mg TU in hypogonadal men. The patient was enrolled in the 1000 mg dosing arm and received the 1st injection of study drug on 16-Jun-2006.</p> <p>On [REDACTED] (b) (6), following an 8th injection of study drug on 29-Jan-2008, the patient suffered a massive stroke and died.</p> <p>Hospital records received on 15-Jan-2009 indicate that the patient was admitted on [REDACTED] (b) (6) with acute mental status changes. He had been speaking with his wife when she stated, "He suddenly stopped talking and looked like he was trying to fall to the right." The event occurred suddenly with no witnessed seizure activity. Upon initial examination, the patient was lethargic but easily aroused and completely globally aphasic. He could not follow commands and had a right facial droop with diffuse weakness on the right side. Diagnostic testing as follows: On [REDACTED] (b) (6) computed tomography (CT) scan of the head without contrast revealed no acute intracranial hemorrhage or mass. Old left inferior cerebellar hemispheric infarction. Hyperdense internal carotid arteries and the middle cerebral arteries of unclear etiology. Unable to exclude a thrombosis of the middle cerebral arteries bilaterally versus these being normal variants. Magnetic resonance imaging (MRI) neck angiogram revealed no significant common carotid or internal carotid artery stenosis identified on either side in the neck. On [REDACTED] (b) (6), a MRI of the head revealed a sub-acute stroke in the distribution of the left middle cerebral artery. Electrocardiogram on admission revealed sinus rhythm with an old left bundle branch block. Initial laboratory results were within normal limits. The neurology consultation impression was acute ischemic stroke in the territory of the left middle cerebral artery (MCA) rule out large vessel. Treatment included tissue plasminogen activator (tPA) with admission to the intensive care unit. The patient's condition deteriorated and he died on [REDACTED] (b) (6). Stroke was listed as cause of death on the death certificate.</p> <p>Event was deemed severe, definitely not related to study drug, and the outcome was death due to a massive stroke.</p> <p>The patient had received an 8th injection of study drug on 29-Jan-2008.</p>				

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<b>Patient ID</b>	<b>Study Number</b>	<b>Site Number</b>	<b>Treatment</b>
078-4162	IP157-001 Part A	078	1000 mg testosterone undecanoate (TU) injections given intramuscular (IM) at 12-week intervals
<p>Concomitant medications taken at time of event included: Allegra, Teveten HCT (600/25), Singulair, Lipitor, Flomax, Flonase, Betamethasone Valerate Foam 12%, Betamethasone Valerate Lotion 1%, Furosemide, Klor-Con, Glucosamine/Chondroitin 1000/500, multivitamin, Advil, Tri-Mix, Cialis, Advil, Gabapentin, Metoprolol, Celebrex, and Zocor.</p> <p>The Investigator assessed the relationship between event and study drug as definitely not related, and the Medical Monitor agreed with the Investigator's assessment.</p>			

**Subject 0001-006020/Study IP157-001B**

Patient ID	Study Number	Site Number	Treatment	
001-6020	IP157-001 Part B	001	1000 mg testosterone undecanoate (TU) given intramuscular (IM) at baseline, at 8 weeks, and then every 12 weeks thereafter	
Age	Race	Sex	Last Treatment Date	
75	Caucasian	Male	11-Jan-2007	
Past Medical History				
Sinusitis, erectile dysfunction, osteoarthritis, mild alopecia, benign colon polyps, anal fissure, urolithiasis, benign prostatic hyperplasia, bladder outlet obstruction, herpes zoster of the face and scalp, secondary hypogonadism, and pilonidal cyst. The patient also experienced an SAE of bone metastasis on 22-Feb-2007.				
Adverse Event		Malignant Neoplasm of Lung		
Onset Date	Severity	Relationship	Outcome	
6-Mar-2007	Severe	Definitely not related	Death	
Narrative				
<p>A 75-year-old Caucasian male (001-6020) was enrolled in Study IP157-001 Part B, a 2-arm, open-label, multicenter pharmacokinetic and long-term safety study of IM injections of 750 mg or 1000 mg TU in hypogonadal men. The patient was enrolled in the 1000 mg dosing arm and received the 1st injection of study drug on 11-Jan-2007. Injections of 1000 mg TU were given at baseline, at 8 weeks, and then every 12 weeks thereafter.</p> <p>On 13-Mar-2007, following the 1st injection of study drug, the patient presented to the Investigator's site for a 2nd injection of study drug. This injection visit was originally scheduled for 9-Mar-2007 but patient had requested a reschedule. The patient complained of back pain radiating to his right leg and that the pain began on 1-Feb-2007. An X-ray of the lumbar spine on 9-Feb-2007 showed moderate to severe degenerative change most marked at the lower lumbar spine, slight loss of normal lordosis, minor multilevel antero-/retrolisthesis, and minor scoliosis which in part may be positional or spasm. An anterior-posterior (AP) pelvis and hips X-ray on 9-Feb-2007 showed mild scattered degenerative change about the hips and bony pelvis. A repeat X-ray of the pelvis on 14-Feb-2007 showed mild degenerative change in the right and left hip, degenerative changes in the lower spine, no focal bony abnormality, and fracture or dislocation. A magnetic resonance imaging (MRI) of the lumbar spine on 22-Feb-2007 showed an abdominal aortic aneurysm measuring slightly over 5.0 cm in size. There were multiple bone lesions at T12-L1 and the sacrum which were very suspicious for metastatic disease, in addition to widespread degenerative changes. A bone scan to further evaluate the skeleton for further lesions was recommended. A bone scan on 28-Feb-2007 showed multiple areas of increased activity consistent with metastatic disease. Computed tomography (CT) of the torso with and without contrast on 6-Mar-2007 showed reticular nodular interstitial thickening in the periphery of the left upper lobe, of indeterminate etiology. Findings may simply represent infection or inflammation. A lymphangitic tumor such as bronchoalveolar cell carcinoma was a much less likely possibility. A 5 cm infrarenal abdominal aortic aneurysm with extensive wall thrombus was noted.</p> <p>The investigator was contacted by the patient's daughter on (b) (6) and was told that the patient expired. The death certificate confirms cause of death as Advanced Lung Cancer.</p>				

Patient ID	Study Number	Site Number	Treatment
001-6020	IP157-001 Part B	001	1000 mg testosterone undecanoate (TU) given intramuscular (IM) at baseline, at 8 weeks, and then every 12 weeks thereafter
<p>The study drug was permanently stopped on 13-Mar-2007. The event was ongoing on 13-Mar-2007. The patient expired on (b) (6)</p> <p>Event was deemed severe, definitely not related to study drug, and the outcome was death on (b) (6)</p> <p>Study drug was permanently discontinued due to this event.</p> <p>Concomitant medications taken at time of event include: Flonase, Cialis, enteric coated aspirin, Celebrex, Motrin, and Percocet.</p> <p>The Investigator assessed the relationship between event and study drug as definitely not related, and the Medical Monitor agreed with the Investigator's assessment.</p>			

**Subject 00078-007012/Study IP157-001C**

Patient ID	Study Number	Site Number	Treatment	
078-7012	IP157-001 Part C	078	750 mg testosterone undecanoate (TU) at 0 and 4 weeks (IM), and every 10 weeks thereafter	
Age	Race	Sex	Last Treatment Date	
45	African American	Male	24-Sep-2007	
Past Medical History				
Hypertension (2005), hypercholesterolemia (2005), conduction defect of LBBB noted on screening electrocardiogram (ECG), mild bilateral gynecomastia (2007), torn ligament right knee with repair (1978), torn ligament left knee with repair (1982), erectile dysfunction (2005), secondary hypogonadism (2005), and seasonal allergies				
Adverse Event		Fatal Myocardial Infarction		
Onset Date	Severity	Relationship	Outcome	
06-Oct-2007	Severe	Definitely not related	Death	
Narrative				
<p>A 45-year-old African American male (078-7012) was enrolled in Study IP157-001 Part C, a single-arm, 2-stage, open-label, randomized multicenter pharmacokinetic and long-term safety study of intramuscular injections of 750 mg TU in hypogonadal males. The patient was administered the 1st injection of study drug on 9-Apr-2007. Injections were given at 0 and 4 weeks, and every 10 weeks thereafter.</p> <p>On 03-Dec-2007, following a 4th injection of study drug on 24-Sep-2007, the site attempted to contact the patient at home concerning his study appointment the next day. On 4-Dec-2007, the site attempted to call the patient at work and reportedly was informed by personnel, "He passed away about a month ago from a massive heart attack." The site located the patient's obituary in a newspaper and confirmed patient had died on (b) (6) at (b) (6).</p> <p>Event was deemed severe, definitely not related to study drug, and the outcome was death.</p> <p>Study drug was discontinued and the outcome of event was death on (b) (6).</p> <p>Concomitant medications taken at time of event included: Diovan, Caduet, Toprol, Viagra, and Levitra.</p> <p>Investigator assessed the relationship between event and study drug as definitely not related, and the Medical Monitor agreed with the Investigator's assessment of study drug relationship</p>				

**Subject 00050-007010/Study IP157-001C**

<b>Patient ID</b>	<b>Study Number</b>	<b>Site Number</b>	<b>Treatment</b>	
050-7010	IP157-001 Part C	050	750 mg testosterone undecanoate (TU) at 0 and 4 weeks (IM), and every 10 weeks thereafter	
<b>Age</b>	<b>Race</b>	<b>Sex</b>	<b>Last Treatment Date</b>	
52	Caucasian	Male	6-Feb-2008	
<b>Past Medical History</b>				
Hypertension (2005), chronic renal insufficiency (2005), non-insulin-dependent diabetes (2005), gout (2005), hypercholesterolemia (2005), pelvic fracture (2001), facial fracture (2001), pilonidal cyst (1978), erectile dysfunction (2006), osteoarthritis (2005), ichthiosis (1960), and primary hypogonadism (2005), drug allergy (penicillin)				
<b>Adverse Event</b>		Cardiac Arrest		
<b>Onset Date</b>	<b>Severity</b>	<b>Relationship</b>	<b>Outcome</b>	
12-Apr-2008	Severe	Remote	Death	
<b>Narrative</b>				
<p>A 52-year-old Caucasian male (050-7010) was enrolled in Study IP157-001 Part C, a single-arm, 2-stage, open-label, randomized multicenter pharmacokinetic and long-term safety study of intramuscular injections of 750 mg TU in hypogonadal males. The patient was administered the 1st injection of study drug on 6-Apr-2007. Injections were given at 0 and 4 weeks, and every 10 weeks thereafter.</p> <p>On [REDACTED] (b) (6), after having received a 6th injection of study drug on 6-Feb-2008, the patient experienced cardiac arrest resulting in death. Death certificate listed cause of death as cardiopulmonary arrest with contributory illnesses of hypertension, cardiovascular disease, and diabetes mellitus. No autopsy was performed.</p> <p>The event was deemed severe and the possibility of relatedness to the study drug as remote.</p> <p>The last dose of study drug was administered on 6-Feb-2008. Death occurred on [REDACTED] (b) (6).</p> <p>Concomitant medications taken at time of event included: Vytorin, Actos, allopurinol, Tricor, Byetta, Lotrel, Celebrex, and Edex.</p> <p>The Investigator has assessed the relationship between event and study drug as remote, and with the information provided, the Medical Monitor agreed with the Investigator's assessment of study drug relationship.</p>				

**Subject 00103-002051/Study 39732 (IPASS)**

Subject ID	Study Number	Site Number	Treatment
2051	39732	Not applicable	Testosterone undecanoate 1000 mg injection (could receive up to 4 injections approximately 8-12 months total)
Age	Race	Sex	Last Treatment Date Before Onset of Adverse Event (AE)
56	White	Male	6-Aug-2007
Past Medical History			
Late-onset hypogonadism, hypertension, hyperuricemia, erectile dysfunction			
Serious Adverse Event	Suicide, cause unknown		
Onset Date	Severity	Relationship	Outcome
15-Nov-2007	Severe	Unlikely	Fatal
Narrative			
<p>A 56-year-old male subject (2051) was enrolled in Study 39732 and received 2 intramuscular injections of testosterone undecanoate 1000 mg for hypogonadism on 25-Jun-2007 and 6-Aug-2007; he did not return for the third injection.</p> <p>The physician contacted the subject's wife, and learned that the subject committed suicide on (b) (6). The wife provided no further information about the suicide.</p> <p>No other AEs were reported during the study.</p> <p>The subject was taking concomitant medications of allopurinol for hyperuricemia, Provas Comp for hypertension, and Levitra for erectile dysfunction.</p> <p>The Investigator assessed the relationship between the completed suicide and study drug as unlikely.</p>			

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**Subject 0001-00039/Study ME97029**

Patient 39 was included in the study because of the condition of hypopituitarism; 25 years old (born (b) (6)), 175 cm, 115 kg; Other relevant history: prolactinoma, obesity

On (b) (6) the patient sustained fatal traffic accident. Riding a motor cycle the inexperienced rider (driving license for 6 months) collided with a truck on wet road and died. The exact cause of the death remains unknown.

Concomitant medication with the indication of prolactinoma was Dostinex® (cabergolin 0.5 mg).

The event occurred after about 9 weeks following the 2<sup>nd</sup> TU application (doses of 1000 mg each) of the follow-up period of the study preceded by 3 TU doses of 1000 mg at 6-week intervals and a 4<sup>th</sup> dose after an interval of 9 weeks during the main study.

The death was assessed by both the investigator and the sponsor as not related to the study treatment.

**Subject 00001-000012/Study NB02**

Follow-up information was received on 17-Dec-2008 from the physician who provided the hospital summary record about the hospitalization from (b) (6) to (b) (6). The reporting physician clarified, that the previously reported unspecified adverse reaction was a sepsis. The patient used Durogesic (fentanyl) as patch for pain therapy. Patient's relevant medical history included a hip-total endoprosthesis (TBP) left 1995 with instable luxation of prosthesis.

Patient's history: In November 2003 the patient developed atonic tetraparesis and acute renal failure in case of spondylodiscitis cervical. Due to persisting complete sensomotoric tetraplegia sub C4 corporectomy of cervical vertebral bodies 5 and 6 with ventral stabilisation C4 to 7 required on (b) (6). During the following course the patient developed decubitus Trochanter on right side which needed several debridement. On (b) (6) a flap closure was necessary. Flap was partly necrosed and generation of fistula required vacuseal treatment.

On (b) (6) the patient was admitted due to paralytic ileus. Cardiac insufficiency, global respiratory insufficiency, hypotension, acidic metabolic imbalance and paralytic ileus have been diagnosed. Patient needed catecholamines and get artificial oxygenation. On 1 (b) (6), the patient was transferred to department of paraplegia for further therapy. Above the right Trochanter major two wounds were visible (size of 3.0 and 4.0 cm in diameter) with fistula and connection to proximal femur. The wounds showed purulent inflammation in marginal region.

Course and therapy: After extended diagnostic measures paralytic ileus was treated conservatively. The patient needed intensive care unit care from (b) (6) to (b) (6) from (b) (6) to (b) (6) and from (b) (6) to (b) (6). Artificial oxygenation and regular bronchoscopy continued. The methicillin-resistant Staphylococcus aureus (MRSA) contamination and infection was treated based on microbial testing with antibiotics. A local wound therapy in region of Trochanter on the right side was done. In the further course of disease patient developed spontaneous septic wound in region of thoracic wall on the left side. Regularly [sic] change of bandages were done. After diagnosis of osteomyelitis of proximal femur, sanitation could not be performed due to critical condition of the patient.

Outcome: Despite intensive medical care the patient died due to sepsis with multi organ failure on (b) (6).

Follow-up information received on 17-Dec-2008 from the physician: The physician once more accentuated that there is no causal relation between the adverse events and Nebido therapy. No change in company assessment. This case is in follow-up.

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### **APPENDIX 3. CASES ADJUDICATED AS ANAPHYLAXIS FROM THE NEBIDO POSTMARKETING SURVEILLANCE DATABASE**

**Case 200711268BNE:** This spontaneous case report was received from a healthcare professional in Great Britain describing a male of unknown age who was receiving Nebido for testosterone deficiency. On an unknown date in 2007, the patient experienced an embolism characterized by cough and dyspnea. He also reported oral discomfort and chest pain. The reaction occurred immediately after the patient was given an injection of Nebido by his wife. The patient was hospitalized for 2 days. No information regarding the duration of symptoms or the treatment given was provided. The patient recovered from the event. It is not known if the patient had received previous therapy with Nebido. The patient has received subsequent doses of Nebido without incident.

**Case 200924735GPV:** This spontaneous case report was received from a healthcare professional in Sweden describing a 22-year-old male patient who had been receiving Nebido since 2006 for Klinefelter's Syndrome without incident. In May 2009, he received an injection of Nebido from his sister-in-law who is a nurse. During the injection, the patient developed dyspnea, a swollen tongue, became scared and started shivering. The patient reported no pruritis and his skin color was normal. In the ambulance he was treated with intravenous adrenalin, intravenous hydrocortisone, and salbutamol. After the adrenalin he began to shiver more and had tachycardia. On admission to the hospital, his pulse was 65 beats per minute and his blood pressure was 140/75 mm Hg. In the hospital he was treated with an antihistamine intravenously and 2 L of intravenous fluids, inhaled ipratropium, and inhaled salbutamol. In addition, he was also given another dose of hydrocortisone intravenously. The patient also received oxygen. The duration of symptoms was approximately 1 hour. The patient remained in the hospital for observation for 1 day. Hospital records further indicated "suspected pulmonary oily microembolism." The patient has received subsequent injections of Nebido without incident.

**Case 2011-016767:** This spontaneous case report was received from a healthcare professional in Great Britain describing a 42-year-old male patient who been receiving Nebido since 2006 after testicular cancer. In 2011, it was reported that immediately after the injection of Nebido the patient developed anaphylactic shock characterized by throat tightness, dyspnea, cough, and a rash. The patient received adrenalin, an antihistamine, and 2 steroids. The breathing improved with the adrenalin. The patient was hospitalized and recovered. The time to resolution of the symptoms was not stated. He was discharged with prednisolone and an antihistamine. The patient had not had a similar reaction to Nebido previously. Nebido therapy was discontinued.

**Case 200932012GPV:** This spontaneous case report was received from a healthcare professional in Australia describing a 16-year-old male patient who had received Reandron for an unknown period of time for testicular agenesis. The patient had received Reandron previously without reaction. On an unknown date in 2009, the patient experienced an anaphylactic reaction, characterized by hyperhidrosis, pruritis, urticaria, throat tightness, angioedema, dyspnea, chest discomfort, cough, and dizziness fewer than 3 minutes after receiving his 3rd injection of Reandron. The patient was treated with steroids, an antihistamine, and oxygen. (It is unclear if the patient received adrenaline.) The patient was taken to the emergency department but was not

hospitalized. No information regarding the duration of symptoms or other treatment given was provided. The patient recovered from the event. The patient had skin testing performed by an allergist. The allergist indicated that this was an atopic individual and that testing he performed demonstrated that his reaction was to benzyl benzoate and not to castor oil or testosterone undecanoate itself. Therapy with Reandron was discontinued.

**Case GB-2007-023826:** This spontaneous case report was received from a healthcare professional in Great Britain describing a 45-year-old male who had been receiving Nebido for hypogonadism. During his 2nd injection in 2007, he developed anaphylaxis characterized by respiratory distress, throat tightness, obstructive airway disorder, cough, wheezing, rash, and pruritis. The patient was treated with epinephrine and an antihistamine in the office and then transferred to the hospital. He was noted to have T-wave inversion, thought to be due to the adrenalin, which reverted to normal. The reaction was considered life threatening. No information regarding the duration of symptoms or treatment given was provided. The patient was discharged from the hospital the same day. It is unknown if therapy with Nebido was continued.

**Case 200815625LA:** This spontaneous case report was received from a healthcare professional (who was also the consumer) in Brazil describing a 60-year-old male who had been receiving Nebido for testosterone deficiency since 2007. In 2008, it was reported that the patient had an anaphylactic reaction, characterized by throat irritation, cough, laryngeal edema, laryngospasm, and dyspnea instantaneously after the Nebido injection. The patient was treated with fluids, adrenalin, steroids, and an antihistamine. He stayed in the office for 2 hours and was then transferred to the emergency department. Hospitalization was advised, however, the patient left after 12 hours of observation. No information regarding the duration of symptoms or other treatment given was provided. The reporter considered the event life-threatening. Treatment with Nebido was discontinued.

**Case 2011-105544:** This spontaneous case report was received from the Regulatory Authority in Sweden describing a 68-year-old male patient who had been receiving Nebido since 2007 for hypogonadism. In October 2011, it was reported that the patient had an anaphylactic reaction, characterized by cough, dyspnea, flushing, dysgeusia, and muscle spasticity during an injection of Nebido. During the previous injection, 3 months earlier, the patient experienced “weak symptoms” (not described). The patient had received 30 injections of Nebido overall. The patient had a past medical history of allergic reactions to bee stings and several foods. He was treated with glucocorticoids, antihistamines, a dopamine agonist, and a calcium channel blocker. His blood pressure remained stable and no skin rash was noted. His symptoms persisted for over 1 hour and slowly improved. The patient recovered. Therapy with Nebido was discontinued.

**Case SE-2006-017516:** The spontaneous case report was received from a healthcare professional in Sweden describing a 47-year-old male who had been receiving Nebido for a hypothalamic-pituitary disorder. Follow-up was provided by the Swedish Medical Products Agency. In January 2006, during the first injection, it was reported that the patient had experienced a swelling of his throat and palpitations. The events resolved spontaneously after 5 minutes. During the second injection in March 2006, the patient experienced hypersensitivity, characterized by pharyngeal edema, palpitations, dyspnea, fatigue, and cough. He had difficulty breathing lasting for

5 minutes and fatigue and cough which lasted for several hours. Therapy with Nebido was discontinued.

**Case 2011-083027:** This spontaneous case report was received from a consumer in Russia which describes a male patient of unknown age receiving Nebido for an unknown indication. While the first milliliter was being injected, the patient experienced an urge to cough. During the second milliliter, the patient started experiencing severe coughing and dyspnea. After the third milliliter, the patient experienced itching, and after the fourth milliliter of the injection, the patient experienced loss of consciousness. The patient took liquid ammonia as corrective therapy. The constellation of symptoms (loss of consciousness, blood pressure decreased to 100/90 mm Hg, itch, difficulty breathing) was considered drug hypersensitivity. The patient took an antihistamine as a treatment for the itching sensation. The patient recovered with the sequelae of skin itch and palate itch. The advice of the patient's allergist was that therapy with Nebido be discontinued.

**Case AT-2006-001317:** This spontaneous case report was received from the wife of the patient describes a 64-year-old male patient who was receiving Nebido for an unknown indication. It was reported that after the 2nd injection of Nebido, the patient developed dyspnea, anxiety, fatigue, sleep disorders, depression, severe hot flushes, and tachycardia (heart rate >109 beat per minute.) Information about the duration of the symptoms and any treatment given was not provided. It is also unknown if therapy with Nebido was continued.

**Case BR-2007-005496:** This spontaneous case report was received from a physician in Brazil describing a 57-year-old male who was receiving Nebido for an unknown indication. It was reported immediately after the 1st injection of Nebido, that the patient had anaphylactic shock characterized by glottis edema, dyspnea, and malaise. The dyspnea became worse 30 minutes after the Nebido injection. He was treated with steroids and "ventilated" in the drug store. The patient's malaise lasted for 3 days. Information about the duration of other symptoms and any additional treatment was not provided. Therapy with Nebido was discontinued.

**Case 2011-110321:** This spontaneous case report was received from the Regulatory Authority in Malta describing a male patient of unknown age who was receiving Nebido for hypopituitarism since 2008. In September 2011, it was reported that the patient had violent coughing during the injection and was close to collapsing. He then developed a generalized maculo-papular rash. The reporter considered these events to be life-threatening. No information was provided regarding the duration of symptoms or any treatment that was provided. Therapy with Nebido was discontinued.

**Case 200916799LA:** This spontaneous case report was received from a healthcare professional in Ecuador describing a male of unknown age who had been receiving Nebido for testosterone deficiency syndrome since January 2009. It was reported that there were no adverse reactions after the first injection. It was reported that the immediately after the 2nd injection, the patient experienced anaphylactic shock characterized by rash and dyspnea. The patient had received the injection from a pharmacist. The patient was treated with intravenous hydrocortisone and recovered. The duration of symptoms was not reported. There is no family history of hypersensitivity. Nebido therapy was discontinued.

**Case 200812881BNE:** This spontaneous case report was received from the Regulatory Authority in Great Britain describing a 27-year-old male who was receiving Nebido for primary testicular failure. Immediately after the 2nd injection of Nebido, it was reported that the patient experienced bronchospasm, cough, felt hot, and was wheezing. The patient's past medical history is significant for asthma. The patient was treated with nebulized salbutamol and recovered after 20 minutes. It is unknown if therapy with Nebido was continued.

**Case 200711462BNE:** This spontaneous case report was received from the Regulatory Authority in Great Britain describing a 44-year-old male who had been receiving Nebido for gynecomastia since March 2007. In November 2007, immediately after the injection of Nebido, the patient experienced cough, dyspnea, and flushing. The patient recovered in 1 day. No information regarding any treatment provided was reported. It is unknown if therapy with Nebido was continued.

**Case 200930704GPV:** This spontaneous case report was received from a healthcare professional in Germany describing a 43-year-old male patient who had been receiving Nebido for an unknown indication since 2005. (The patient's past medical history included Klinefelter's Syndrome.) In June 2009, during the injection of Nebido, it was reported that the patient had dyspnea, urticaria, and had a sensation of heat. The patient was treated with steroids and the symptoms began to subside in 30 minutes and the patient was fully recovered in 1 hour. There is no familial history of allergy. Therapy with Nebido was discontinued.

**Case 2011-018006:** This spontaneous case report was received from the Swiss Regulatory Authority describing a 61-year-old male patient who had been receiving Nebido since November 2009 for an unknown indication. In April 2010, after the 3rd administration of Nebido the patient experienced a type 1 hypersensitivity reaction characterized by cough, dyspnea, wheezing, facial edema, an erythematous rash, and an increase in blood pressure. He was treated with an antihistamine, intravenous steroids, and salbutamol spray. The events lasted for 30 minutes. The patient recovered. Therapy with Nebido was discontinued.

**Case 201047159GPV:** This spontaneous case report was received from the German Health Authority via a report on their internet web page describes a 63-year-old male patient who was receiving Nebido for testosterone deficiency syndrome. In September 2010, the patient developed a type I hypersensitivity reaction characterized by a hot flush, cough, and bronchospasm. This was the patient's 2nd injection of Nebido. The patient's past medical history included asthma. The patient was treated with intravenous anaphylaxis therapy (not otherwise specified,) and quickly improved. The patient recovered after 20 minutes. The reaction was considered to be life-threatening. Nebido was administered 1 additional time and a worsening of symptoms was noted. Therapy with Nebido was discontinued.

**Case 201040508GPV:** This case report from a clinical trial was reported by the Investigator in Germany who was conducting an Investigator-sponsored phase 1 double-blind study to evaluate the allergic potential of Nebido and formulation components. The report describes a male patient of unknown age who was receiving Nebido for an unknown indication. After the 1st injection of 0.4 mL of Nebido, the patient developed reddening of the skin, an increase in blood pressure (from 150/100 mm Hg to 205/130 mm Hg 30 minutes after the injection), a feeling of flushing, and dyspnea. The patient was treated with corticosteroids and antihistamines. The reaction resolved within 20 minutes. The patient recovered. In accordance with the protocol, the patient

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was observed overnight. Rechallenge was stated to be positive. It is unknown if therapy with the full dose of Nebido was ever given.

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#### **APPENDIX 4. CASES ADJUDICATED AS INDETERMINATE FROM THE NEBIDO POSTMARKETING SURVEILLANCE DATABASE**

**Case 200815181GPV:** This spontaneous case report was received from a healthcare professional in Germany describing a 52-year-old male who had been receiving Nebido for decreased testosterone since 2004. In 2008, it was reported that the patient had an assumed micro fat embolism, characterized by headache, dyspnea, feeling hot, throat irritation, and syncope at an unspecified time after the Nebido injection. The reaction lasted about 20 seconds. The patient was treated with intravenous fluids. The patient was hospitalized in the intensive care unit and was discharged the following day. Chest computed tomography (CT) did not reveal infarction or bleeding. No information regarding the duration of symptoms or other treatment given was provided. The patient recovered from the event. The patient has had numerous doses of Nebido since this event without incident.

**Case 200818230LA:** This spontaneous case report was received from a healthcare professional in Brazil describing a 58-year-old male patient who had been receiving Nebido for hormone replacement therapy. It was reported that the patient had an anaphylactic reaction at an unspecified time after the first Nebido injection and was hospitalized. No information was provided as to the patient's symptoms. No information regarding the duration of symptoms or the treatment given was provided. The patient recovered from the event. It is unknown if therapy with Nebido was continued.

**Case 200819576LA:** This spontaneous case report was received from a healthcare professional in Brazil describing a male unknown age who was receiving Nebido for an unknown indication. It was reported that the patient had hyperhidrosis, cough, facial erythema, and dizziness. It is unknown if the patient received any therapy at the time of the event. The time to the onset and duration of symptoms was not reported. The patient has received additional injections of Nebido without incident.

**Case 200828604GPV:** This spontaneous case report was received from a healthcare professional in Germany describing a 41-year-old male patient who was receiving Nebido for Klinefelter's Syndrome for 6 years. It was reported that during the injection the patient had an anaphylactic reaction characterized by chest discomfort, cough, eye irritation, flushing, and a tingling sensation which started in the lungs and ascended to the nose. The patient was treated with steroids, an antihistamine, and ranitidine. After 30 minutes, the patient recovered. The patient had skin testing with the components of Nebido which were negative, while histamine control yielded a skin reaction of +4/10. However, further therapy with Nebido was discontinued.

**Case 200912293BNE:** This spontaneous case report was received from a healthcare provider in Great Britain describing a 53-year-old male patient who was receiving Nebido for hypogonadism for approximately 2 years. In this single case report, 2 separate episodes of adverse reactions are reported. During the first episode, it was reported that the patient had mild anaphylactic shock characterized by throat irritation, dyspnea, and flushing. It was also noted on the form that the patient had pulmonary microemboli with the same symptom complex as described. The time to onset of the reaction and any treatment that may have been provided are not noted in the report.

The patient recovered. With the second episode, 12 weeks later, it was reported that immediately after the injection, the patient had anaphylactic shock characterized by throat tightness, throat irritation, hyperhidrosis, erythema of the face, dyspnea, flushing, an irregular heart rate, and bronchospasm. It was also reported that the patient had pulmonary fat emboli characterized by throat tightness, throat irritation, hyperhidrosis, and erythema. It was reported that the patient may have been treated with hydrocortisone. The patient recovered 45 to 60 minutes later. Nebido was discontinued.

**Case 200912294BNE:** This spontaneous case report was received from a healthcare professional in Great Britain describing a 32-year-old male patient who was receiving Nebido for hypogonadism for approximately 2 years. It was reported that the patient had anaphylactic shock characterized by feeling abnormal, throat tightness, dyspnea, panic attack, flushing, and bronchospasm. It was also reported that the patient had a fat embolism with the same symptom complex. No information regarding the timing of the injection and the appearance of the symptoms was noted. The reporter does not think that the patient received any therapy. The time to resolution of symptoms was not reported. The patient recovered. In the same report it was noted that the patient may have had a reaction to the previous injection of Nebido characterized by an odd feeling, tightening of the throat, shortness of breath. It was described as a bit like a panic attack. The day that episode occurred the patient was taken to the emergency department. No information regarding the timing of the injection and the appearance of the symptoms was noted. No information about any treatment that may have been given or the time until the resolution of symptoms was noted. Nebido was discontinued.

**Case 200940933GPV:** This spontaneous case report was received from a healthcare professional in Germany describing a 37-year-old male patient who was receiving Nebido for Klinefelter's Syndrome for approximately 1 year. It was reported that 4 minutes after the injection, the patient had a hypersensitivity reaction characterized by hyperhidrosis, syncope, nausea, tachycardia, hypotension, dyspnea, and anxiety. He was treated with 250 mL saline solution and an intravenous steroid. The patient's symptoms resolved within 7 minutes. The patient recovered. Therapy with Nebido was continued without incident on subsequent injections.

**Case 200942732GPV:** This spontaneous case report was received from a healthcare professional in Germany describing a 62-year-old male patient who was receiving Nebido for hypogonadism and had had 14 injections in total. It was reported that the patient experienced malaise, feeling hot, cough, and stridor during injection 13. No information regarding the onset of symptoms, any therapy that may have been given or the time to resolution of acute symptoms was reported. It was stated that the patient recovered within 3 months. At the time of the next injection, the patient experienced a sensation of heat and cough during the injection, and the injection was interrupted after less than 1 mL had been injected. It is unknown if therapy with Nebido was continued.

**Case 201018709GPV:** This spontaneous case report was received from a healthcare professional in Austria describing a 40-year-old male patient who was receiving Nebido for an unknown indication for approximately 1 year. It was reported that immediately after receiving Nebido, the patient experienced circulatory collapse (blood pressure decreased), cough, and dyspnea. The patient did not have urticaria. It was unknown if the patient had pruritis or a skin rash. No therapy for the event was given. It was reported that the patient recovered after approximately 30 minutes. Therapy with Nebido was discontinued.

**Case 201021482GPV:** This spontaneous case report was received from a healthcare professional in South Africa describing a 63-year-old male patient who was receiving Nebido for hypogonadism. He had received previous injections without any reaction. It was reported that with his 3rd and 4th injections, the patient experienced an anaphylactic reaction characterized by cough, dyspnea, anxiety, presyncope, tachycardia, and decreased blood pressure. The patient was treated with oxygen and intramuscular steroids, but was not hospitalized. No information was provided relating to the onset of symptoms or the duration of symptoms, but full recovery was reported. It is unknown if therapy with Nebido was continued.

**Case 201029358GPV:** This spontaneous case report was received from a urologist in Germany describing a male patient approximately 44 years of age who was receiving Nebido for hypogonadism for an unknown period of time. It was reported that immediately after the injection of Nebido, the patient had anaphylactic shock characterized by redness of face, malaise, paresthesia, cough, and chest discomfort. It was further reported that “anaphylactic shock was assumed.” No information was reported about any treatment that the patient may have received. The patient recovered after 30 minutes. It was subsequently reported by a consulting allergist that no allergy testing was done, instead implicating “suspicion of POME”. It is unknown if therapy with Nebido was continued.

**Case 201035276GPV:** This spontaneous case report was received from the Regulatory Authority in Great Britain describing a 45-year-old male patient who was receiving Nebido an unknown indication for approximately 4 years. It was reported that the patient had an anaphylactic reaction, no characterization was provided. No information regarding the onset of the reaction, any treatment that may have been given, or the duration of symptoms was provided. It was reported that the patient recovered. Therapy with Nebido was discontinued.

**Case 201041966GPV:** This spontaneous case report was received from a healthcare professional in Denmark describing a 42-year-old male patient who was receiving Nebido an unknown indication for an unknown period of time. It was reported that the patient had anaphylactic shock, no characterization was provided. No information was provided regarding the onset of symptoms, any treatment that the patient may have received, or the time to resolution of the symptoms. It is unknown if therapy with Nebido was continued.

**Case 201042008GPV:** This spontaneous case report was received from a healthcare professional in Sweden describing a 61-year-old male patient who was receiving Nebido for hypogonadism for an unknown period of time. The report contains information about 2 separate incidents. Approximately 1 minute after the injection, it was reported that the patient had cough and pharyngeal edema. The patient was given water and all symptoms improved within 10 minutes. The patient had never had a reaction to Nebido before this time. The following month the patient had another injection of Nebido and described similar symptoms of cough and pharyngeal edema. There was no dyspnea reported for either event. The onset of this reaction as reported to the patient to the nurse was 1.5 hours. It is unknown if therapy with Nebido was continued.

**Case 2011-002167:** This was a spontaneous case report from a male consumer of unknown age in Ghana who was receiving Nebido for hormone replacement therapy for approximately 3 years. The patient reported that within seconds of starting the injection he developed an overwhelming need to cough, constriction in airway, and difficulty breathing. The episode lasted for

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approximately 10 minutes. It is not known if any treatment was given. It is unknown if therapy with Nebido was continued.

**Case 2011-011368:** This spontaneous case report from the health authority in Great Britain describes a 41-year-old male patient prescribed Nebido for an unknown indication who experienced an anaphylactic reaction characterized by dyspnea, rash, and throat tightness, which was considered life threatening. Treatment provided for the event was reported as oxygen, adrenaline, chlorphenamine, and hydrocortisone, and the patient recovered. Further details were not provided. It is unknown if therapy with Nebido was continued.

**Case 2011-040546:** This spontaneous case report from a physician in Brazil refers to a male patient of unknown age who received Nebido for an unknown indication. Approximately 1 or 2 minutes after the injection of Nebido, the patient experienced difficulty breathing, dizziness, vertigo, darkened vision, joint pain, sweating, weakness, pallor, decreased temperature, and absence of autonomy. All events were reported to have recovered. It is unknown if therapy with Nebido was continued.

**Case 2011-046164:** This spontaneous case report was received from the Spanish Regulatory Authority describing a case of a 34-year-old male who had received Reandron for years for an unknown indication. In May 2011, on the day of the injection but at an unspecified time after the injection of Reandron, the patient developed dyspnea, cough, depressed level of consciousness, muscular weakness, pallor, and hyperhidrosis. He was treated with adrenaline and oxygen and he improved, however, his symptoms started again and he was taken to the hospital for observation. The following day, the patient had recovered and he was discharged from the hospital. It is unknown if any other treatment was given. It is unknown if therapy with Reandron was continued.

**Case 2011-087892:** This was a spontaneous case report received from the regulatory authority in Great Britain describing a 50-year-old male who had been receiving Nebido for impotence since approximately April 2009. In September 2009, it was reported that immediately after the injection of Nebido, the patient developed dyspnea, a burning sensation in his hands and feet, oral discomfort, musculoskeletal pain, cold sweat, pallor, syncope, and pain in an extremity. He was placed in a supine position and an antihistamine was given with little effect. He was transported to the hospital where he was treated with nitroglycerin and aspirin. In the hospital his blood pressure was 126/92 mm Hg, pulse was 100 and he had a normal electrocardiogram (ECG). No other information was provided with respect to the duration of the symptoms, any additional treatment which was provided in the hospital or the time of discharge. It is unknown if therapy with Nebido was continued.

**Case 2011-090820:** This spontaneous case report from a pharmacist in Germany describes a male patient of unknown age who was receiving Nebido for an unknown indication for an unknown period of time. It was reported the patient developed anaphylactic shock after injection. No information regarding the onset of symptoms, any treatment that was given, or the time of resolution of symptoms was provided. The patient recovered. It is unknown if therapy with Nebido was continued.

**Case 2011-108268:** This spontaneous case report from a pharmacist in Austria describes a 51-year-old male patient receiving Nebido since 2008 for hypogonadism (post-surgical and radiation therapy for seminoma). During an injection of Nebido in 2011, the patient experienced

allergic reaction, dizziness, pressure sensation at the esophagus, dyspnea, prickle sensation of the throat, sneezing, vertigo, and cough. Conflicting information regarding the previous Nebido injections is noted (reported as good toleration, elsewhere reported as “same as the feeling during previous Nebido injections”). It is unknown if therapy with Nebido was continued.

**Case AT-2007-035468:** This spontaneous case report from a physician in Austria documents a 46-year-old male patient under treatment with Nebido since 2005 for orchitis/testosterone deficiency, who in 2007 experienced anaphylactic reaction characterized as “like gag irritation and trickle [sic] of the throat”. This reaction occurred 30 seconds after Nebido injection. The patient was treated with an oral antihistamine. The patient recovered within 15 minutes. The patient did receive a subsequent uneventful dose, divided between left and right gluteal injections.

**Case DE-2005-004016:** This spontaneous case report from Germany from a consumer describes a male patient of unknown age who received 2 doses Nebido for hypogonadism. Approximately 15 seconds after the second injection of Nebido, it was reported that the patient experienced circulatory collapse with several minutes unconsciousness described further with nausea, tickling cough, and defecation. No information was provided regarding the duration of symptoms or if the patient received therapy. The patient recovered. It is unknown if therapy with Nebido was continued.

**Case DE-2005-008181:** This spontaneous report from Germany was received from a physician regarding a 67-year-old male patient with obesity prescribed Nebido for hypogonadism. With the first injection of Nebido (exact time not specified) the patient developed an allergic reaction, described as circulatory collapse, nausea, retching, and fever attacks. The main symptom of circulatory collapse was reported as decrease of blood pressure, although there was “no exact measurement during event”. No information regarding the duration of symptoms or any treatment that may have been given was provided. Nebido therapy was withdrawn.

**Case DK-2005-009832:** This spontaneous case report from Denmark was received from a physician, and describes a male of unknown age who was receiving Nebido for testosterone deficiency. It was reported that 3 minutes after the first injection of Nebido, the patient experienced knee and foot arthralgia, intensive cough, chest pain, a systemic burning feeling, and pruritus in the palate. The patient’s symptoms resolved within 20 minutes. No information is provided as to any treatment that might have been given. It is unknown if therapy with Nebido was continued.

**Case ZA-2007-035469:** This spontaneous case report was received from a healthcare professional from South Africa describing a 29-year-old male patient with cerebral palsy and muscular atrophy who was receiving Nebido for hypogonadism. It was reported that within a minute of receiving a Nebido injection, the patient developed what was described as a life-threatening anaphylactic reaction characterized by bronchospasm, circulatory collapse, decreased blood pressure, syncope, and pallor. Upon admission to the hospital, his blood pressure was 111/74 mm Hg, heart rate was 100, and his oxygen saturation was 94%. He was treated with intravenous hydrocortisone and nebulized adrenalin. The time to resolution of his symptoms was not noted. The patient was observed for 2 hours and discharged. At the time of discharge his oxygen saturation was 99%. It is unknown if therapy with Nebido was continued.

**APPENDIX 5. SERIOUS ADVERSE EVENT – CASE 379-000024**

Patient (Set)	Patient number: 24 (b) (6)		Study site / Investigator:	
Demographic data (Screening)	Age: 50 years		Race: Caucasian	
	Weight: 90.0 kg	Height: 180 cm	BMI: 27.8 kg/m <sup>2</sup>	
Nature and timing of SAE	Investigator's term: <b>1) Psychovegetative exhaustion</b> <b>2) Circulatory collapse after physical overload</b>		HARTS term: 1) Central nervous system disorder 2) Shock	
			MedDRA preferred term: 1) Autonomic nervous system imbalance; 2) Circulatory collapse	
CIOMS No.: DE-2006-032458 Event verbatim: Other serious criteria: Medically significant Psychovegetative exhaustion [Autonomic nervous system imbalance] ([Sleep disorder]); Circulatory collapse after physical overload [Circulatory collapse]; Furuncle on back [Furuncle]; Allergic swelling of knee after insect bite [Allergy to arthropod bite]				
Start – End of treatment: 04 Sep 2003 – 06 Jun 2006				
Date of SAE: 1) Feb 2006 2) Mar 2006		Time after SOT: 1) (can not be calculated) 2) (can not be calculated)		
End of SAE: 1) - 2) Mar 2006		Outcome: 1) Not recovered 2) Recovered		
<b>SAE description</b>				
<p>A clinical trial investigator reported the occurrence of circulatory collapse due to exhaustion after physical overload in this male patient with a history of hypogonadism (left-sided testicular reduction) who started the study treatment on 04 Sep 2003. The patient had received 14 i.m. TU injections altogether between 04 Sep 2003 and 06 Jun 2006.</p> <p>The patient's medical history included testicular varicocele. Concurrent medical conditions were arterial hypertension since Jul 2005, hypercholesterolemia known since 15 years despite sports, and overweight (BMI of 28.7 kg/m<sup>2</sup>). The patient suffered from hyperhidrosis axillaris on both sides which had improved with testosterone administration. Concomitant medication included LISINAPRIL taken since 2002 for hypertension.</p> <p>The patient was hospitalized in a rehabilitation clinic (b) (6) due to psycho-vegetative exhaustion with sleeping disturbances (since Feb 2006); he reported to fall asleep not before midnight and normally sleep through for 5 to 6 hours, after awakening he could not get to sleep again. The patient complained about severe occupational stress and reported that he had experienced syncope of unknown cause in Mar 2006 (cardiac causes could not be proven). The patient had taken a sauna on the day before (3 procedures) and had been on a strenuous hike on the same day. Concurrent diagnoses on admission to hospital included a furuncle on the back and allergic swelling of the right knee after insect sting. Abnormal laboratory tests on admission included increased total bilirubin value of 1.59 mg/dl and increased serum C-reactive protein (CRP) value of 11.9 mg/l.</p> <p>ECG performed on (b) (6) showed normal results. Ultrasound of the thyroid gland on (b) (6) showed homogenous tissue and a total volume of 26 mL. Small cysts up to 3 mm in diameter were seen in the left lobe. The patient was treated with L-tryptophan (Kalma) 4x500 mg in the evening for sleep disorder and received physiotherapy (including medical training therapy), psychotherapy, and Jacobson's progressive muscle relaxation therapy. An improvement of the sleep disorder and the psycho-vegetative exhaustion was achieved following these therapy measures. Initial local treatment of the furuncle with Ichtholan ointment was not effective, thus antibiotic treatment with amoxicillin 2x1 g for 7 days was added. The insect sting reaction was treated with Fenistil gel (locally) and calcium (per oral) 2x500 mg per day. The patient was discharged from hospital on (b) (6).</p>				

(Continued)

Continued: SAEs Autonomic nervous system imbalance and Circulatory collapse in Patient 24			
<b>Characteristics of SAEs</b>			
<b>Intensity</b>	1) + 2) Moderate	<b>Drug treatment</b>	1) Yes; 2) No
<b>Main pattern</b>	1) + 2) Continuous	<b>Non-drug treatment</b>	1) Yes (Hospitalization, psychotherapy, physiotherapy); 2) No
<b>Study drug action</b>	1) + 2) Dose not changed	<b>Outcome</b>	1) Not recovered; 2) Recovered
<b>Assessment of drug relationship of SAE</b>			
<b>- by the investigator</b>	Causality as reported: <b>None</b> .		
<b>- by the sponsor</b>	<p>“Psychovegetative syndrome is not an expected adverse reaction to TU, neither is sleeping disorder which was primarily reported as adverse event and is a symptom of psycho-vegetative exhaustion. TU is not known to cause psycho-vegetative exhaustion. On the contrary, testosterone has protective effects on the nervous system and its function. [Bialek M, Zaremba P, Borowicz KK, Czuczwar SJ. Neuroprotective role of testosterone in the nervous system. Pol J Pharmacol. 2004 Sep-Oct; 56(5):509-18. Review.] [Moffat SD. Effects of testosterone on cognitive and brain aging in elderly men. Ann N Y Acad Sci. 2005 Dec;1055:80-92. Review.]. Short-term administration of high-dose testosterone shortens sleep and worsens sleep apnea in older men. No similar effect has been found for longer-term lower-dose androgen therapy on sleep and breathing so far. [Liu PY, Yee B, Wishart SM, Jimenez M, Jung DG, Grunstein RR, Handelsman DJ. The short-term effects of high-dose testosterone on sleep, breathing, and function in older men. J Clin Endocrinol Metab. 2003 Aug;88(8):3605-13.]. This patient had been on study drug for nearly 3 years. The dose of TU was to restore physiologic testosterone levels. Therefore a causal role of TU in the development of psycho-vegetative exhaustion with sleep disorder is unlikely. Syncope is not an expected adverse reaction to TU. Based on its pharmacological properties, a causal role of the study drug is not plausible. More likely is a connection of the reported events with the occupational stress and physical overload as suggested by the investigator. Furthermore there may be links with hypertension and obesity, both conditions present in this patient.</p> <p>Causality as determined: <b>Unlikely</b>.”</p>		

## **APPENDIX 6. SUMMARY OF RISK MANAGEMENT APPROACH IN THE EUROPEAN UNION FOR NEBIDO (TESTOSTERONE UNDECANOATE)**

In the European Union, pulmonary oil microembolism (POME) and hypersensitivity/anaphylaxis reactions are both recognized in the 2008 EU-Safety Risk Management Plan (EU-SRMP). POME is categorized as an Important Identified Risk whereas hypersensitivity/anaphylaxis reactions are classified as Important Potential Risks. (Note: In the 2013 EU-SRMP submission hypersensitivity/anaphylaxis reactions were reclassified by Bayer at the request of the Periodic Safety Update Report (PSUR) Assessor as an Important Identified Risk; however, the Final Assessment Report to confirm this classification has not been issued by the Health Authorities.) Both POME and anaphylaxis are addressed under the EU-SRMP by pharmacovigilance and risk minimization activities as described below.

Language regarding POME has been included in the EU Summary of Product Characteristics (SmPC) since the first marketing authorization was approved in November 2003. The EU SmPC was updated in 2008 based on clinical and postmarketing experience, with the respective wording on POME added to the Undesirable Effects<sup>1</sup> section of the EU SmPC. Routine pharmacovigilance is conducted for POME events including a cumulative evaluation in PSURs if relevant new cases are reported and cumulative review of spontaneous data for possible delayed POME reactions. Additional pharmacovigilance includes estimation of frequency of POME in non-interventional studies. The routine risk minimization activities include warnings in the EU SmPC, specific risk minimization recommendations (strictly intramuscular and very slow injection), a description of typical clinical characterizations of POME, and patient management recommendations.<sup>2</sup> Additional risk minimization activities with respect to POME include continuing existing educational activities at scientific conferences and enhancing current written and audio-visual educational materials distributed to prescribers and other healthcare professionals.

Since the first marketing authorization, the EU SmPC has listed hypersensitivity as a contraindication (which is standard for EU SmPCs), and in the most recent EU SmPC suspected anaphylactic reactions is listed in the warnings and precautions section, and suspected anaphylactic reactions and hypersensitivity are listed as Undesirable Effects.<sup>3</sup> The routine

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<sup>1</sup> Pulmonary microembolism of oily solutions can in rare cases lead to signs and symptoms such as cough, dyspnoea, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia, or syncope. These reactions may occur during or immediately after the injection and are reversible. Cases suspected by the company or the reporter to represent oily pulmonary microembolism have been reported rarely in clinical trials (in  $\geq 1/10,000$  and  $< 1/1,000$  injections) as well as from postmarketing experience.

<sup>2</sup> As with all oily solutions, Nebido must be injected strictly intramuscularly and very slowly (over 2 minutes). Pulmonary microembolism of oily solutions can in rare cases lead to signs and symptoms such as cough, dyspnoea, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia, or syncope. These reactions may occur during or immediately after the injection and are reversible. The patient should therefore be observed during and immediately after each injection in order to allow for early recognition of possible signs and symptoms of pulmonary oily microembolism. Treatment is usually supportive, eg, by administration of supplemental oxygen.

<sup>3</sup> Suspected anaphylactic reactions after Nebido injection have been reported.

pharmacovigilance activities include a cumulative evaluation in PSURs if additional new cases are reported and additional pharmacovigilance activities include estimation of frequency in non-interventional studies. Routine risk minimization consists of the information in the SmPC, as noted above.