SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Vaniqa. This scientific discussion has been updated until 1 July 2004. For information on changes after this date please refer to module 8B.

1. Introduction

Vaniqa, with the active ingredient eflornithine hydrochloride monohydrate, an amino acid analogue, is intended for the treatment of facial hirsutism in women. Vaniqa is to be applied to the affected areas twice daily.

Eflornithine hydrochloride is an irreversible inhibitor of the enzyme ornithine decarboxylase (ODC). ODC is responsible for the catalysis of ornithine to putrescene, and is a critical enzyme for cell proliferation and function. Follicular cell proliferation and synthetic functions are important factors in hair growth. As ODC is present in the hair follicle, and implicated in the growth process, eflornithine has been developed as a topical product to treat facial hirsutism in women. In view of the reported rapid turnover of ODC and the short half-life of eflornithine, continuous treatment is required. An intravenous form has been available for the treatment of West African trypanosomiasis (*T. brucei gambiense*).

Hirsutism is the presence of excess hair growth in women and should not be considered, by itself, a disease. Although the condition may indicate an underlying disorder of androgen production (e.g. polycystic ovary syndrome), in most cases hirsutism results from a combination of mildly increased androgen production and increased skin sensitivity to androgens ('idiopathic' hirsutism). Not all hirsutism is androgen-dependent. Androgen-independent hirsutism can be inherited as a familial trait. In addition, drugs such as steroids, cyclosporin, diazoxide and phenytoin, can cause hirsutism.

There are many levels of hirsutism severity. If of minor severity it is often considered to be a cosmetic problem. However if of sufficient severity, it may have social and psychological influences on women. The amount of hair a woman will tolerate before it becomes unwanted varies considerably both culturally and racially. Women of Indian or Negroid origin tend to have less facial or body hair compared with Caucasians. Among Caucasians, women of Mediterranean origin tend to have a heavier hair growth than those of Nordic origin.

The usual forms of treatment are mechanical hair removal (shaving, plucking, waxing, and depilatory creams) and medical treatment. Electrolysis and laser therapy are expensive but effective methods of permanent hair removal. Mechanical methods alleviate the problem temporarily but may result in local irritation. Medical treatment consists mainly of suppressing ovarian (oral contraceptives) or adrenal androgen secretion or of blocking androgen in the skin (e.g. cyproterone acetate). The potential for systemic side-effects limits the use of these treatments.

There is a need for a safe and effective topical treatment for female facial hirsutism.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

The cream contains 15% w/w eflornithine hydrochloride monohydrate (eflornithine) corresponding to 11.5% w/w eflornithine anhydrous in an oil-in-water emulsion for topical administration. The excipients consist of water (solvent), glyceryl stearate and polyethylene glycol-100 stearate (emulsifiers), cetearyl alcohol and ceteareth-20 (emulsifiers), phenoxyethanol/methylparahydroxybenzoate/ propylparahydroxybenzoate (preservative system), stearyl alcohol (gelling agent), with mineral oil and dimethicone as emollients.

The product is packaged in 15g, 30g and 60g tubes (blend of high density and low density polyethylene), with a polypropylene screw cap.

Active substance

Information on the active substance has been provided in the form of an EDMF for each site of manufacture.

Eflornithine is a racemic mixture, with no chiral reagents used during synthesis. Data for 19 batches demonstrates the absence of chiral (optical) activity. Eflornithine can exist in 3 physical forms A, B or C at ambient conditions confirmed by spectroscopic and thermal studies. Form C is the thermodynamically most stable form and the one routinely produced by the method of synthesis as defined in the dossier. However, as the drug substance is in a solution prior to mixing and remains solubilised in the final product, the different polymorphs are not an issue for product bioavailability. Proof of structure is provided using IR spectroscopy (in water); ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR, and elemental analysis.

There are no unknown impurities present at levels above 0.1%. Six known impurities have been identified at levels less than 0.1% with a further degradation product also controlled by the specification (each impurity ≤ 0.1%).

The identification of eflornithine is based on IR. The purity is controlled by HPLC. The impurity limits in the specifications are justified by the toxicology studies.

A total of 21 batch analysis results have been presented. Data comply with specifications.

Thermal and light stress testing has been performed on eflornithine as solid substance as well as in aqueous solutions. From these studies it can be concluded that eflornithine dry substance is stable towards high temperatures but should be protected from light. The major degradation products formed during the studies were identified. Data was presented for six batches of product (three at each site) investigated at 25°C/60% RH, 30°C/60% RH and 40°C/75% RH. Data support a retest period of 12 months.

Other ingredients

Methyl and propyl parahydroxybenzoates, phenoxyethanol, stearyl alcohol, dimeticone and purified water, all comply with the relevant Ph.Eur. monographs. Certificates of analysis are provided for these ingredients and are acceptable. A statement is provided to the effect that these materials do not contain, and are not derived from specified risk material as defined in Commission Decision 97/534/EEC. A similar statement has been provided regarding the non-pharmacopoeial ingredients.

The non-pharmacopoeial ingredients consist of mineral oil, and two proprietary excipients. These latter two excipients consist of a mixture of cetearyl alcohol and ceteareth 20, and a mixture of glyceryl stearate and polyethylene glycol 100 stearate. Specifications and certificates of analysis are provided for these ingredients. The mineral oil used in the preparation meets the Ph.Eur. purity requirements, but does not meet the Ph.Eur. viscosity requirement. It does, however, meet all NF requirements for light mineral oil. The specifications provided are acceptable.

Product development and finished product

Eight different formulations (including three placebo formulations) were used in the clinical trials. One of the formulations is identical to that to be marketed and three other formulations (containing 5, 10 and 15% of eflornithine, equivalent to 3.83, 7.67 and 11.5% anhydrous hydrochloride free) are very similar to the marketing formulation except that a modified preservative system was included. The last formulation is entirely different from that to be marketed, a water/ethanol mixture is used as solvent and no emulsifiers or preservatives are included.

The crystalline forms A, C and mixtures of these have been used in pre-clinical and clinical studies. From solubility studies it was evident that the three crystal forms have the same aqueous solubility at the temperatures studied (room temperature and 65°C, which is the temperature used to dissolve the substance). Independently of crystal form the substance dissolves within 5 minutes and does not recrystalize when frozen. As the drug substance is easily dissolved during manufacture independently of morphic form this is not an issue for the bioavailability of the substance.

The particle size distribution of the drug substance varies from batch to batch as demonstrated by light scattering measurements. Since the substance is easily and completely dissolved this parameter is not critical for product manufacture or for the bioavailability of the active substance.

The preservative system was optimised at a 0.4% level in the formulation. To ensure that the product is adequately preserved throughout its shelf life, the product was challenged at the reduced level of preservative of 70%, 80% and 80% of its initial level of phenoxyethanol, methyl parahydroxybenzoate and propyl parahydroxybenzoate, respectively, and the results indicate a satisfactory capacity to withstand microbial contamination even with low levels of preservatives.

The product is being manufactured in a facility that holds the necessary Manufacturing Authorisation.

The control tests and specifications for the finished product are adequately drawn up, and are considered to be relevant for a product of this type. The identification of eflornithine is based on HPLC.

Specifications for microbial purity for the finished product are included in the release and shelf-life specifications and conform to the requirements of the European Pharmacopoeia.

The results from 4 pilot scale batches and two of smaller size have been submitted. The data presented clearly indicates uniformity of mixing for the active and each preservative at pilot scale (10% of proposed commercial scale). Impurities have not been detected except for one batch, which utilised a different test method.

Stability of the product

The applicant has provided data from 23 stability studies performed on 10 batches (seven of these are of at least pilot scale). Five of the pilot scale batches are manufactured at the intended site.

The conclusion from the studies is that there is no significant degradation of the finished product at any of the conditions studied (5°C, 25°C/60% RH, 30°C/60% RH, 40°C, 50°C, 40°C/75% RH, light studies, and freeze/thaw conditions). Concerning accelerated studies the provided data package do not fulfil the ICH requirements (CPMP/ICH/380/95), three batches of at least pilot scale manufactured at the intended site and stored for at least 6 months at 40°C/75%RH. For a third batch data is provided for 12 weeks of storage at 45°C/75%RH. However there are enough data from supporting stability testing to confirm the stability of the finished product throughout the proposed shelf life of 2 years.

Apart from quantitation of eflornithine, preservatives and related substances other parameters, including appearance, viscosity, weight change and pH have been monitored. The analytical methods used are the same as those used for release testing of the finished product.

There is no evidence of interaction between the product and the packaging container.

The stability data presented are satisfactory and support the proposed shelf life of 2 years when stored below 25°C, as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

Vaniqa cream is manufactured using a conventional manufacturing process. The chemical-pharmaceutical dossier is well documented and guarantees the quality of the active substance and finished product, both initially and throughout the shelflife. The proposed specifications are suitable and relevant for a topical product of this type. A number of quality points were not resolved at the time of the CPMP opinion. However, these were considered to be minor, without any impact on the efficacy or safety of the product, and are indicated to be addressed post-approval.

3. Part III: Toxico-pharmacological aspects

Eflornithine has been developed as an ornithine decarboxylase inhibitor.

In the following text the strength of eflornithine is expressed both as the monohydrate chloride form and as the anhydrous form.

Pharmacodynamics

In vitro studies

Eflornithine *in vitro* inhibited ornithine decarboxylase (ODC) activity in hamster epididymal cytosol. The results were confirmed *ex vivo* where treatment of male Syrian golden hamsters with eflornithine 2% (equivalent to 1.52% anhydrous hydrochloride free) significantly inhibited ODC in the cytosol of hair follicles. Hence, an indication of *in vivo* penetration of eflornithine was noted at a concentration lower than the 15% cream formulation (equivalent to 11.5% anhydrous hydrochloride free) proposed for marketing.

In vivo studies

A variety of dosages, vehicle formulations and treatment times were used in the studies in animal models of hair growth using the Syrian golden hamster and mice, which to some extent can explain the disparity in obtained results. Therefore, no conclusion can be drawn regarding the most effective dose/concentration of eflornithine. In one study, the dose-response profile of eflornithine (1-10%) was investigated in the Syrian golden hamster after 21 days of treatment. Maximum reduction of hair mass (-50%) was obtained with a 2% eflornithine (equivalent to 1.52% anhydrous hydrochloride free) formulation. In another study, also performed in the golden hamster, comparable results were found with 5, 10 and 15% eflornithine (equivalent to 3.83, 7.67 and 11.5% anhydrous hydrochloride free), resulting in 85% hair mass inhibition. In mice, a dose dependent reduction in hair growth was observed after treatment with eflornithine 1-15% (equivalent to 0.76-11.5% anhydrous hydrochloride free). Apart from the differences in these results, it is evident that eflornithine induces a marked reduction in hair growth rate of both daily and total hair lengths. The reduction in hair mass was partly reversible when investigated in a 42 days reversibility study. The reversibility of hair growth is not immediate, although during withdrawal of treatment, the ODC level returned to baseline within 24 hours.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been performed.

General pharmacology

No studies on general pharmacodynamics have been performed.

Pharmacokinetics

The pharmacokinetics of radiolabelled or non-radiolabelled eflornithine was determined in mice and rats after single topical or oral administration. In addition, dermal permeability of eflornithine was investigated *in vitro* in guinea pig and human cadaver skin. Pharmacokinetic parameters after repeated oral dosing were investigated in toxicology studies in rats.

The limit of quantification (LOQ) by LC-MS-MS was 5 ng/ml (equivalent to 3.83% anhydrous hydrochloride free) for rat plasma. In K_3EDTA samples, the LOQ was 2.5 ng/ml (equivalent to 1.92% anhydrous hydrochloride free) for mouse, rat and human plasma.

The absorption of eflornithine is complete (100% of dose) in dogs or nearly complete (90% of dose) in rats following oral administration.

In mice, following oral administration, the pharmacokinetics were linear over a wide dose range (10-2000 mg/kg (equivalent to 7.67-1533.2% anhydrous hydrochloride free)).

Terminal plasma half life is 6 hours in the mouse following intravenous or oral administration and 6-8h following dermal application.

Systemically absorbed eflornithine is rapidly excreted unchanged via the renal route in mice, rats and humans.

When using skin permeation techniques *in vitro*, the dermal absorption of eflornithine was 1.6% in guinea pig, and 0.2% in human cadaver skin.

Dermally applied radiolabeled eflornithine to male and female mice passed the stratum corneum when investigated with tape stripping techniques. The highest levels of radioactivity found 4 hours after

dosing were in the skin test site, kidneys, lungs, urinary bladder, liver, stomach and small intestine. After 24 hours, eflornithine related radioactivity was found at the skin test site and the kidneys. Radioactivity was still present at the skin test site, large intestine and kidneys 96 hours after dosing, although the levels were decreasing with time.

After application of the cream base formulation intended for marketing as a single dermal dose (approximately 600 mg/kg, equivalent to 459.96% anhydrous hydrochloride free) to mice, the systemic absorption was less than 0.84% of the dose administered. In female rats treated dermally twice daily (approximately 30 mg/kg/dose, equivalent to 23 mg/kg/dose anhydrous hydrochloride free) the dermal absorption was less than 0.75% after up to 5 days of treatment, but 3-4% after 7 days of dermal dosing. In another study in rats, no difference in absorption was observed between male and female rats after both oral and dermal administration of eflornithine.

In rats, which were treated topically twice daily for 1-7 days, the concentration of drug derived radioactivity increased during the 7-day dermal dosing period. Apart from the skin test site, radioactivity was found in the urinary bladder, kidneys, pituitary gland and spleen after 7 days of dermal dosing. Following oral dosing (7 days of single oral doses), the highest concentration of drug related radioactivity was found in the intestine, kidneys, adrenals and liver. Ninety-six hours after the last dose, low amounts could still be detected especially in the kidneys and liver.

Eflornithine does not bind to plasma proteins.

Eflornithine is decarboxylated by ornithine decarboxylase *in vitro*. However, no metabolism of eflornithine has been observed *in vivo* and no metabolism studies have been performed.

Toxicology

Single dose toxicity

In acute oral and dermal toxicity assessed in rabbits and rats respectively eflornithine showed very low acute toxicity. However, autopsies were not performed and therefore no determination of target organ toxicity could be made.

Repeat dose toxicity

A two-week, a six-month and a one-year toxicity study of eflornithine were performed in mice, rats and minipigs. The six-month study in rats compared the toxicity of eflornithine to vehicle. Based on dosages the animals received approximately 25 (rat) and 75 (minipig) times the intended clinical dose in humans.

The two-week study in mice was a limited study in which no autopsies or biochemical/haematological measurements were made. No clinical or dermal effects were observed in either group of animals over the 14-day observation period.

In the six-month study in rats in which the 10% eflornithine solution (equivalent to 7.67% anhydrous hydrochloride free) and 15% eflornithine cream (equivalent to 11.5% anhydrous hydrochloride free) were applied transient, very slight, reversible erythema of the treatment site was noted initially in animals treated with either the 15% eflornithine cream (equivalent to 11.5% anhydrous hydrochloride free) or its corresponding vehicle control. No local effects on the skin were observed in rats treated with the 10% eflornithine solution (equivalent to 7.67% anhydrous hydrochloride free) or the vehicle solution. No other treatment related effects were observed neither during the study nor at necropsy. There were no signs of systemic toxicity. The concentrations of the compound in rat plasma were below the limit of detection.

In minipigs 15% eflornithine lotion (equivalent to 11.5% and 115 mg/kg as anhydrous hydrochloride free) was applied twice daily for 1 year corresponding to 15 and 150 mg/kg eflornithine daily (equivalent to 11.5% and 115 mg/kg as anhydrous hydrochloride free). No deaths or treatment-related clinical findings were noted, except reduced hair growth from week 23 onwards. The only significant haematological findings were an increase in RBC, Hb and haematocrit during week 39 in male pigs only. These alterations were not seen at any other time period or in female animals and were not considered to be toxicologically relevant. There were no treatment-related changes in bodyweight gain, physical or ophthalmic parameters, clinical chemistry, organ weights or histopathology. The NOEL was considered to be > 150 mg/kg/day (equivalent to 115 mg/kg/day as anhydrous hydrochloride free).

Genotoxicity

Eflornithine was not genotoxic in the standard genotoxicity test battery *in vivo* and *in vitro* at concentrations in the in vivo study 1000 times above clinical exposure.

Carcinogenicity

Two carcinogenicity studies in mice were performed, one 'conventional' and one photocarcinogenicity study. In the 'conventional' study, the animals were treated with dermal application of eflornithine 150, 300 and 600 mg/kg (equivalent to 115, 230 and 460 mg/kg anhydrous hydrochloride free). When calculating on exposure, the animals were exposed hundreds/thousand fold above clinical exposure already at the lowest dosage. There were no product related changes in survival, clinical observations, body weights or food consumption. No treatment related findings were noted at necropsy except acanthosis and hyperkeratosis of the treated skin without dermal irritation, observed especially in female mice in all dosage groups except the untreated control. The incidence and severity was relatively even across the vehicle control and treatment groups, except for a slight increase at high dose level. Hence, these findings seem to be caused by the vehicle, although an additive effect by eflornithine at high dose level can not be ruled out. No difference in neoplastic changes (including skin tumours) between the groups was observed.

In the photocarcinogenicity study, hairless mice were treated for 40 weeks with 60, 180 and 600 mg/kg of eflornithine (equivalent to 46, 138 and 460 mg/kg anhydrous hydrochloride free) topically, plus subjected to ultraviolet radiation (UVR). Untreated control groups received UVR at two different radiation intensities, which induced a dose-related response in development of skin tumours (shorter duration of tumour onset and increased tumour yield). An enhanced tumour response was also observed in the group receiving the vehicle lotion plus UVR (600 RBU/week) compared to the group receiving only UVR. After application to skin areas of a moisturising cream, less reflection of light occurs and a higher amount of light is penetrated into the skin, which might explain the higher incidence of tumours observed in the vehicle control group. Mice that received eflornithine showed a reduced skin tumour development compared to those administered the vehicle lotion.

In response to the List of Questions the results of two oral carcinogenicity studies in rats and mice performed by the National Cancer Institute were submitted. Eflornithine was not carcinogenic after oral administration to mice for 2 years at doses up to 1000 mg/kg/day (equivalent to 767 mg/kg/day anhydrous hydrochloride free) (Johnson 2000) and not carcinogenic after oral administration to rats of eflornithine for 2 years at doses up to 600 mg/kg/day (equivalent to 460 mg/kg/day anhydrous hydrochloride free) (Crowell 2000).

Reproduction toxicity

The reproduction toxicity studies were performed in rats and rabbits. Eflornithine was in most studies administered to the animals via the dermal route. In the peri/postnatal study in rats, drinking water was used as route of administration.

Eflornithine had no effect on male or female fertility investigated in rats at exposure levels approximately 500-1000 times above clinical exposure in the high dose group.

Two embryotoxicity studies with topical application to rats were performed. In one study severe toxicity of the embryos/foetuses was observed in both treatment groups. The incidence of live foetuses and weights in surviving foetuses was low. Skeletal malformations (delayed ossification) and soft tissue variations (dilatation of the lateral ventricles of the brain and increased renal pelvic cavitation) were observed. These findings were probably caused by oral ingestion of the test compound since no precautions were taken to prevent oral exposure of the cream. The study was repeated under such precautionary measures and no treatment related findings on either maternal or litter parameters were observed except skin reactions (erythema). Toxicokinetic data from the HD group demonstrated an exposure approximately 5-25 times (depending on time of measurement) less than in the first study. Hence, the toxicokinetic data support the assumption of suspected oral ingestion of the test substance in first study. The animals were exposed considerably (500-1000 times) above clinical exposure.

In the rabbit embryotoxicity study, the high dose level (150 times the intended clinical dose) caused severe maternal toxicity (prolonged reductions in body weight gain (≈ 10%) and food consumption, severe skin reactions at the application sites and one death/four abortions). Necropsy demonstrated an

increase in implantation loss and a decreased foetal body weight in this group. In response to the List of Questions and List of Outstanding Issues the applicant submitted a preliminary report on a seven-day pharmakokinetic study in pregnant rabbits. The study showed an adequate safety margin (>500 the exposure) for use in man.

The peri/postnatal study in rats demonstrated slight maternal toxicity (reduction in body weight gain and food consumption) at doses ≥ 190 times the intended clinical dose. A decrease in mean pup weight was noted in mid and high dose groups while other parameters related to gestation, pup survival and development were normal except a slight decrease in fertility of the high dose F1 generation. These results can, however, be accepted considering the high oral doses used in the study and the low systemic absorption of eflornithine following dermal administration of eflornithine cream.

Local tolerance and special toxicity studies

The dermal irritating potential of different cream formulations, among them the one proposed for marketing, was tested in a number of studies in New Zealand White rabbits. The duration of the studies was between 5 and 14 days. In general, information on the concentration of the active compound was lacking. All formulation tested resulted in mild to moderate irritation. The 15% cream formulation (equivalent to 11.5% anhydrous hydrochloride free) was also tested in mice (13 weeks) and hamsters (13 days). No indications of systemic toxicity (mice) or dermal irritation (mice, hamsters) were seen.

In guinea pigs, a 10% eflornithine solution (equivalent to 7.67% anhydrous hydrochloride free) was nonsensitizing. No phototoxicity was observed in guinea pigs after application of a 15% eflornithine solution plus 1 hour exposure to UVA light.

The primary eye irritation potential was investigated in rabbits. A 10% eflornithine solution (equivalent to 7.67% anhydrous hydrochloride free) or the 15% cream formulation (equivalent to 11.5% anhydrous hydrochloride free) was administered to washed and unwashed eyes of the rabbits. Mild to moderate (conjunctival) irritation potential was observed in both washed and unwashed eyes.

Environmental Risk Assessment

An assessment of the environmental risk was performed and no significant risk to the environment related to the use of eflornithine is anticipated.

Discussion on toxico-pharmacological aspects

Several deficiencies regarding the preclinical investigation of systemic toxicity of eflornithine have been identified, i.e. lack of investigation of target organ toxicity in acute dosing and lack of safety pharmacology studies. However, considering the low systemic exposure and the absence of clinical safety concerns based on experience from long-term use of high oral doses this can be accepted. Daily doses of eflornithine 1 g/day (equivalent to 0.76 g/day anhydrous hydrochloride free) has been administered orally to humans for one year without significant toxicity in most patients.

It is concluded that eflornithine is not genotoxic and does not seem to have carcinogenic or photocarcinogenic potential. However, the vehicle used in the photocarcinogenicity study, which with only minor differences is similar to the vehicle intended for marketing, induced an enhanced tumour response. In response to the List of Questions the applicant argued based on a literature survey that topically applied vehicles can alter the properties of the skin (decrease the amount of light reflected, scattered, or absorbed by the skin or increase the extent and/or depth of penetration into the skin of humans and mice). Hence, an increased amount of light can be absorbed which might lead to skin tumour development. A comparison between the vehicle used in the formulation proposed for marketing, and other vehicles, is not possible from the literature data submitted by the applicant. However, there is no indication that this vehicle formulation is worse than other widely used formulations. Therefore, it is concluded that the vehicle of Vaniqa, like other vehicles, can alter skin properties that during UV exposure can lead to enhanced skin tumour formation in mice.

4. Part IV: Clinical aspects

Vaniqa is proposed for the treatment of facial hirsutism in women. Eflornithine is an irreversible inhibitor of the enzyme ornithine decarboxylase (ODC), which is present in the hair follicle and implicated in the growth process. Efficacy and safety has been evaluated in a dose ranging study (GMEH-3071) and two pivotal, multicentre, randomised, vehicle controlled studies (DE140-001, DE140-002). In addition, one supportive, open label study (GMEH-2664) and two long-term open label studies (DE140-010, DE140-011) were presented. The total number of subjects who received eflornithine in the phase II and III studies (including the additional studies) is 1,487 patients out of the enrolled 1721 patients.

In the following text the strength of eflornithine is expressed both as the monohydrate chloride form and as the anhydrous form.

Clinical pharmacology

The pharmacodynamic and pharmacokinetic properties of eflornithine were investigated in both healthy volunteers and patients with facial hirsutism. The 6 studies enrolled a total of 343 subjects applying eflornithine for up to 37 consecutive days. The studies were conducted in compliance with GCP.

Overview of trials presenting pharmacokinetic and/or pharmacodynamic data is given in the table below:

Human Dermal Safety Studies and pharmacokinetic studies

Protocol No.	Phase	Study Design	No. of patients enrolled (Active/Veh)	No. of patients Completed	Formulation Number
DE140-004	I	Repeated Insult Patch Test	230 (230/230)	208	203522-M-03-B*
DE140-005	I	21-Day Cumulative Irritation	30 (30/30)	28	203522-M-03-B
DE140-006	I	Photocontact Allergy	30 (30/30)	28	203522-M-03-B
DE140-007	I	Phototoxicity	25 (25/25)	25	203522-M-03-B
GMEH 2971	I	Pharmacokinetics, radiolabeled, parallel study	18 (18/0)	18	SP33 10%, SP106A 15%, SP106B 10%
DE140-003	I	Pharmacokinetic, open-label radiolabeled	10 (10/0)	10	203522-M-03-B*

Pharmacodynamics

Local irritant effect

DE140-004

In this open, single-centre study 230 healthy individuals were enrolled to determine the contact allergy sensitisation potential of eflornithine. Each subject was exposed to both eflornithine 15% cream (equivalent to 11.5% anhydrous hydrochloride free) and vehicle on different skin sites. Occlusive patches were left in continuous contact with the skin for three weeks and fresh test material applied 3 times per week during this period. Following a two-week no-treatment rest period, a single challenge application was made.

Both the active cream and the vehicle seem to be skin irritants when applied under occlusion. Although eflornithine 15% cream (equivalent to 11.5% anhydrous hydrochloride free) does not seem to cause allergic sensitisation, the possibility cannot be ruled out.

DE140-005

This was a 21-day long open-label skin irritant study including 30 healthy volunteers (25 females, 5 males). Eflornithine 15% cream (equivalent to 11.5% anhydrous hydrochloride free, vehicle cream and a known skin irritant, sodium lauryl sulfate (SLS), were applied under occlusive patches for 21

days on the subject's back. Evaluation of the exposure sites for skin irritancy was done on a daily basis during this period.

Tukey's Studentized Range Test for multiple comparisons indicated the irritation scores for all three test products were significantly different from one another. The highest score was for SLS, followed by eflornithine 15% cream (equivalent to 11.5% anhydrous hydrochloride free) and the vehicle cream. Eflornithine 15% cream (equivalent to 11.5% anhydrous hydrochloride free) was classified as "irritating", the vehicle cream as "moderately irritating" and SLS as "extremely irritating.

Photoallergy-toxicity

DE140-006

This was an open-label photocontact allergy test of healthy subjects. Five males and 25 females were enrolled and the duration of treatment 37 days. Twenty-eight individuals completed the study. Application of eflornithine 15% cream (equivalent to 11.5% anhydrous hydrochloride free and vehicle cream twice weekly for 24 hours during a three-week induction period followed by exposure to ultraviolet light (UVA and UVB). Following a period without treatment, a single application of test substances was made of untreated skin sites and thereafter irradiated with UVA light.

The results of the study do not indicate any tendency for photoallergic reactions caused by the eflornithine 15% (equivalent to 11.5% anhydrous hydrochloride free) cream. However, according to the protocol, 2 MEDs (minimal erythema dose) of unfiltered light from a defined UV source, were used for the irradiation of test sites during the induction phase. Prior to entry of study each individual was tested for MED values. However, several individuals in both treatment groups did not reach a score of even a slight erythema after irradiation of untreated skin with 2 MEDs, especially during the first study week.

DE140-007

This was an open-label study of healthy individuals (22 females and 3 males). A single application of the eflornithine 15% (equivalent to 11.5% anhydrous hydrochloride free) cream or vehicle was applied on a single occasion onto tape-stripped skin sites followed by irradiation with 0.5 MEDs of UVB and to UVA for a duration of 10 times the MED equivalent. Responses were graded on a 5-point scale. Subjects acted as their own controls in that each individual had both test products applied and also an untreated irradiated skin site.

There seems to be no indication of a phototoxic potential. The gradings of erythemal reaction after irradiation appears to be similar for treated and untreated skin.

Pharmacokinetics

The pharmacokinetic documentation for Vaniqa consists of two pharmacokinetic studies (GMEH 2971, DE140-003) and published data from three studies on i.v. and oral eflornithine.

The systemic absorption of eflornithine 15% (equivalent to 11.5% anhydrous hydrochloride free) after topical administration appears low. The estimated absorption based on urine and faecal recoveries of radiolabelled drug after single and multiple dosing were 0.34% and 0.82% of the dose, respectively. Based on LC/MS analysis of urine the mean amount of the dose excreted renally was 1.3% at steady state. The total recoveries (including unabsorbed drug from the application site) were 72.4% and 85.4% respectively and thus, approximately 30 and 15% of the dose were not accounted for. Considering that the radiolabelled drug was administered topically, the recovery is considered fairly high.

The steady state plasma half-life of eflornithine was approximately 8 hours. Steady state was reached within 4 days. Measurable plasma levels of eflornithine are obtained and the mean maximum and trough levels are approximately 10 and 5 ng/ml (equivalent to 7.67 and 3.83 anhydrous hydrochloride free), respectively. After 7 days treatment with eflornithine cream twice daily the maximum levels of eflornithine were approximately twice as high on the last day compared with the first day. The data indicate no major concerns with respect to accumulation of eflornithine after topical administration. Although no data are available for longer treatment periods even a large increase in absorption over time would not be of concern for the safety of Vaniqa given the low systemic absorption and the much lower doses used compared with other indications.

The dose of eflornithine used for the treatment of sleeping sickness is according to published data in the range of 25-30 g per day (equivalent to 19.2-23 g/day anhydrous hydrochloride free), administered i.v. or orally. No maximum daily dosage has been given in the SPC for topical treatment with Vaniqa. In one clinical study, the mean amount of cream applied was approximately 0.5 g (0.383 g anhydrous hydrochloride free) per day, which contains 75 mg (57.5 mg anhydrous hydrochloride free) eflornithine. Doses used to treat sleeping sickness would then be 300-400-fold the daily dose of Vaniqa. Considering an absorption of approximately 1%, the difference would be even larger. The maximum plasma levels of eflornithine after repeated topical administration of 0.5 g (0.383 g) 15% cream twice daily were up to 15 ng/ml (about 80 nM, equivalent to 11.5 ng/ml (about 61.3 nM) anhydrous hydrochloride free). In a Phase I study in cancer patients, systemic effects (decreased polyamine excretion in urine) were observed with C_{max} values of eflornithine between 2.8 µg/ml (15 µM) and 58 µg/ml (320 µM, equivalent to 2.2 µg/ml and 44.5 µg/ml (11.5 and 245 µgM) anhydrous hydrochloride free). These data indicate that the safety margins for topical eflornithine in comparison with i.v. or oral administration are high.

According to published data, eflornithine is mainly eliminated by excretion of unchanged drug in urine. Thus, increased plasma levels after topical administration cannot be completely excluded in patients with severe renal impairment, despite the low systemic absorption.

Studies in special populations

No separate studies have been carried out in special populations, like the elderly, subjects of different races or subjects with renal or hepatic disease. The pharmacokinetic studies were performed in the target population, i.e. females with hirsutism. Eflornithine is mainly excreted unchanged in urine. However, the applicant has estimated that a subject with an 80% reduction in creatinine clearance would obtain a 5-fold higher systemic exposure to eflornithine after topical administration. Compared to the high exposures after systemic administration, the predicted increase in a renally impaired patient is not a safety concern.

Interaction studies

No interaction studies were initially performed with Vaniqa since it is a product for topical use and the systemic exposure to the drug is low. However, in response to the List of Questions the company submitted results from *in vitro* inhibition studies of eflornithine with recombinant human cytochrome P450 isoenzymes. The studies showed that eflornithine is not an inhibitor of metabolism by these enzymes and the likelihood of drug-drug interactions of eflornithine with their respective substrates is low.

Clinical efficacy

The clinical efficacy and safety studies were conducted according to GCP. The design, duration, the number of patients and the demographic characteristics of these patients are given below:

Overview of clinical studies

Protocol No.	Study design and treatment duration	No. of patients enrolled (Active/Veh)	No. o f patients completed	Demographics
GMEH 2664	Open-Label, twice daily, 24 weeks, 12 weeks post treatment follow-up	30 (30/0)	24	24-40 years (32.2 years) 100% White
GMEH 3071	Dose-ranging, double-blind, vehicle controlled, 24 weeks, application twice daily and a follow-up 8 weeks	125 (92/33)	106	20-30 years (26.3 years) 91% White, 7% Black, 2 % Other
DE140-001	Pivotal, double-blind, vehicle-controlled 24 weeks of treatment followed by an 8-week no-treatment phase	287 (190/97)	209	19-74 years (43.4 years) 59% White, 29% Black, 9% Hispanic/Latino, 2% Other, 1% American/Alaskan Native
DE140-002	Pivotal, double-blind, vehicle-controlled 24 weeks of treatment followed by an 8-week no-treatment phase	309 (205/104)	228	18-83 years (41.7 years) 67% White, 28% Black, 4% Hispanic/Latino, 1% Other
DE140-010	Open-Label, 12 months, followed by a 4 week no-treatment phase	216 (216/0)	142	19-77 years (42.5) 76% White, 15% Black, 6% Hispanic/Latino, 1% Asian/Pacific islanders, 1% Other 1% American/Alaskan Native
DE140-011	Open-Label, 6 months, followed by a 4 week no-treatment phase	754 (754/0)	578	18-80 years (41.3 years) 68% White, 13% Black, 15% Hispanic/Latino, 3% Asian/Pacific islanders, 1% American/Alaskan Native, 2% Other

Dose-response studies and main clinical studies

Dose-response study (GMEH-3071)

The study was double-blind with parallel groups treated with 5%,10 %, and 15% eflornithine (equivalent to 3.83, 7.67 and 11.5% anhydrous hydrochloride free) and placebo. The study period was 24 weeks with application twice daily and a follow-up 8 weeks after cessation of therapy.

A total of 187 potential patients with facial hirsutism were screened and of these 125 subjects were included in the study.

Efficacy was measured by using a modification of the Ferriman-Gallwey (mFG) scoring method (5-point scale for each of the parameters length, area, opacity and stiffness) and by video microscopic image analysis of the chin area. Subject self-assessment and subject reports of time spent on hair removal were also reported. Prior to entry the subjects were selected by grading based on mFG chin area score for their hirsutism.

There was a statistically significant reduction of mFG scores for length (but not for area, opacity and stiffness) at the end of treatment compared with placebo (p=0.0001) only for the 15% eflornithine ((equivalent to 11.5% anhydrous hydrochloride free) cream but not for the other formulations. For 15% (equivalent to 3.83, 7.67 and 11.5% anhydrous hydrochloride free) eflornithine cream the absolute difference from baseline was –0.61 (from 3.09 $\pm$ 0.53 to 2.48 $\pm$ 0.69 of a score 0-4), the score 3 represents definite visible and the score 2 represents barely visible. If all four mFG scores were summarised the difference was still significant (p=0.0027) at the end of treatment. This effect was reversed 8 weeks post-treatment. A statistically significant reduction of growth rate (0.19 mm difference in growth length measured after 48 hours ± 6 hours) compared with placebo (p=0.0022) was also detected by the image analysis 25 weeks after initiating therapy with the eflornithine 15%

(equivalent to 3.83, 7.67 and 11.5% anhydrous hydrochloride free) cream only. There were no significant differences between groups for any subject perception parameter at week 25. The 15% eflornithine (equivalent to 3.83, 7.67 and 11.5% anhydrous hydrochloride free) cream formulation was chosen for further studies.

Main clinical studies (DE140-001 and DE140-002)

Both studies were multicentre, double-blind, parallel and vehicle-controlled. Altogether 596 female subjects with excessive facial hair were enrolled. Using a sample size ratio of 2:1, 395 subjects were treated with the proposed market formulation of eflornithine and 201 received treatment with the vehicle. Study medication was applied to facial areas affected by excessive hair growth twice daily for 24 weeks, followed by a period of 8 weeks with no treatment. Only subjects who had a clinical diagnosis of facial hirsutism, a customary frequency of removal of facial hair of two or more times per week and a chin and upper lip hair density of at least 5 terminal hairs per square centimetre (video image analysis) were included in the study.

Between 24-31% of the included population had an endocrine/metabolic history but the figures were comparable for the two treatment groups. Nine individuals who received eflornithine cream and four individuals who received the vehicle presented with a medical history of polycystic ovarian disease. Women taking oral contraceptives were accepted for inclusion.

Primary efficacy endpoint of both studies was the Physician's Global Assessment (PGA). This was an evaluation of the extent of improvement/worsening of the patient's facial hirsutism compared with an initial pre-treatment evaluation. Hair parameters such as length of hairs, density of hairs and darkening of the skin were considered, though not separately ranked. The PGA was performed 48 hours after supervised shaving using a four-point scale: clear/almost clear, marked improvement, improved and no improvement/worse.

Secondary efficacy endpoints were Subjects Self-Assessment Questionnaire (SSAQ) and Video Image Analysis (VIA).

The SSAQ consisted of six questions on the impact of facial hair on the quality of life. The subjects responded to these questions by rating on an analogue scale ranging from 1-100 mm. The 0 point was labelled "not bothered/uncomfortable" and the 100 point was labelled "extremely bothered/uncomfortable".

A video fibre optic microscope was used to collect images of the skin including hair on the treatment sites. Images were transferred to an image analysis system for evaluation of hair growth (length) and spatial mass (hair area).

The primary endpoint, PGA, was dichotomised into success (clear/almost clear or marked improvement) and failure (improved or no improvement/worse). A difference between the treatments groups at week 24 of 20% (based on an expected rate of success of 30% for eflornithine and 10% for vehicle) was prospectively defined to be clinically significant. Differences between treatment in the proportion of subjects achieving success were analysed by the Cochran Mantel-Haenszel test and when the sample of the cell-sizes was small, exact tests such as Fisher's exact test were used.

For the secondary endpoint, the Subject's Self-Assessment, in which the responses to the six questions were expected to be intercorrelated, a multivariate analysis of variance (Wilk's Criterion) was performed with treatment and investigational site as effects in the model to test the null hypothesis that the treatment vectors of means were equal. It this test was statistically significant, a univariate analysis for each question was evaluated.

The other secondary endpoint, reduction of hair growth and spatial mass evaluated by Video Imaging Analysis, was dichotomised into "success" if the reduction of hair growth was at least 50% and "failure" if the reduction was < 50%. Due to small samples of the cell-sizes, the differences between treatments for achieving success were analysed by Fisher's Exact Test. An analysis of variance (ANOVA) was used to analyse treatment differences in spatial mass. ANOVA was also used as an a posteriori analysis for hair growth.

Two data sets were formed for the purposes of efficacy evaluation. One was All Subjects Randomised (ASR) which was the primary data set, which comprised all subjects randomised into the study and who received at least one dose of study medication. The other data set was the Evaluable data set,

which consisted of all subjects who were without significant protocol violations. For both data sets all subjects withdrawn from the studies had their last observation carried forward (LOCF). The distribution of the patients is given below.

	DE 140-001		DE 140-002	
	Vaniqa	**Vehicle**	**Vaniqa**	**Vehicle**
Number of patients randomised, who received medication	188	97	205	104
Number of patients included in the ASR data set for PGA	176	92	198	101
Number of patients in the EDS	166	85	186	95

The reasons for discontinuation were similar for the two treatment groups within each study. The total percentage of the study population who discontinued varied between 24% to 27% for the eflornithine-treated group and between 25% to 28% for the vehicle-treated group. Seven subjects in the vehicle group and three in the eflornithine group requested to discontinue due to lack of efficacy.

For the primary efficacy parameter (PGA) a statistically significant difference of improvement in favour of eflornithine 15% (equivalent to 3.83, 7.67 and 11.5% anhydrous hydrochloride free) cream over vehicle was seen during the treatment period from week 4 and onwards in study DE140-001 and from week 8 and onwards in study DE140-002. Following the cessation of therapy, the drug effect decreased and no statistical significance versus vehicle was seen after 8 weeks. The percentage of subjects who had at least some improvement in the PGA reached a plateau after 8 weeks of treatment. However, the degree of improvement continued to increase throughout the study with more subjects achieving success throughout the study.

Number (%) of Subjects Evaluated as a Success (i.e. clear/almost clear or marked improvement)

	DE140-001			DE140-002		
Week	**Vaniqa n (%)**	**Vehicle n (%)**	**P-value***	**Vaniqa n (%)**	**Vehicle n (%)**	**P-value***
2	7 (4.0)	1 (1.1)	0.273	1 (0.5)	0 (0)	1.000
4	10 (5.6)	0 (0.0)	0.017	19 (9.8)	6 (5.9)	0.258
8	24 (13.5)	3 (3.2)	0.007	40 (20.6)	5 (5.1)	≤0.001
16	36 (20.3)	0 (0.0)	≤0.001	67 (34.2)	5 (5.2)	≤0.001
24	43 (24.4)	4 (4.3)	≤0.001	87 (43.9)	13 (12.9)	≤0.001
32	15 (10.8)	3 (4.3)	0.123	20 (12.9)	5 (6.7)	0.151

*Cochran Montel-Haenszel test (where cell sizes were sparse, exact tests were used)

Distribution of PGA dichotomized into success (i.e. clear/almost clear or marked improvement) at the end of treatment (Week 24) in ASR data set

	DE 140-001		DE 140-002	
	Vaniqa n=176	**Vehicle n**= 92	**Vaniqa n** =198	**Vehicle n**= 101
Total Success (no of patients clear/almost clear and with marked improvement)	43	4	87	13
Success Rate	24.4 %	4.3 %	43.9 %	12.9 %
95% CI	18.3%-31.5%	1.2%-10.8%	36.9%-51.2%	7.0%-21.0%

The statistical difference between Vaniqa and the vehicle was also seen for the data set comprising all randomised patients and the data set of evaluable patients.

Post hoc data of all categories of any improvement were summarised (this was not the primary efficacy measure) and at the end of treatment there were 118 subjects (67%) in the eflornithine 15% cream group compared with 36 subjects (39%) in the vehicle group in DE 140-001. Of subjects treated

in DE 140-002 with eflornithine 15% cream, 73% versus 44% of subjects treated with the vehicle had a PGA, which showed at least some improvement.

For DE 140-001 a treatment-investigator interaction logistic analysis showed that no statistically significant treatment-investigator interaction could be detected. For the study DE 140-002 the treatment-investigator interaction logistic analysis indicated the presence of a statistically significant treatment-investigator interaction (p=0.059). However, the interaction was evaluated to be quantitative rather than qualitative and therefore the data were deemed poolable.

Analysis of prognostic factors for DE 140-001 such as effects of age, race and prior hair removal technique upon the primary response measure demonstrated an effect of race only. The success rate for whites at Week 24 was 30.6% and for non-whites 13.8% as assessed according to the PGA evaluation dichotomised into success at the end of treatment. This success rate was 24.4% for the whole study population. A 50% (3 out of 6) success rate was seen for individuals above the age of 65 years. However, the sample size was too small to verify an age-dependent difference. Prior hair removal techniques did not appear to have prognostic significance. For DE140-002 analysis of prognostic factors upon the primary response measure demonstrated a tendency for a lower success rate for non-whites (34.9%) compared with whites (46.2%), however the difference is not of the same magnitude and significance as in study DE140-001. According to the demographic data for the study population there were no statistically significant differences between treatment groups. A 55.6% success rate was seen for individuals above the age of 65 years as compared with 43% < 65 years of age but again, the sample size was too small to verify an age-dependent difference.

For the secondary efficacy endpoint, SSAQ, mean baseline scores in both study DE 140-001 and DE 140-002 for all six self-assessment questions were over 77 units in both treatment groups. For DE 140-001 examination of the univariate results from the individual questions constituting the questionnaire revealed significant baseline differences for two of the questions. To adjust for this initial bias a multivariate analysis of covariance using these two significant baseline questions as covariates was performed on the assessment at all post-baseline periods. There was a significant difference for all six questions in favour of the eflornithine-treated group compared with the vehicle group (multivariate Wilks test, p= 0.0297) in DE 140-001 and in DE 140-002 (multivariate, p<0.003).

Analyses of subjects self-assessment at week 24

	DE 140-001			**DE 140-002**		
SSAQ question	Vaniqa Mean (SD)	Vehicle Mean (SD)	p-value	Vaniqa Mean (SD)	Vehicle Mean (SD)	p-value
Bothered by facial hair?	64.91 (30.1)	75.83 (24.1)	0.0046	51.91 (31.6)	74.18 (28.2)	0.0001
Uncomfortable when meet new people?	64.10 (31.5)	77.72 (22.7)	0.0005	50.51 (32.7)	71.13 (31.0)	0.0002
Uncomfortable at work or class?	63.83 (23.8)	74.41 (23.9)	0.0011	48.46 (32.6)	68.81 (30.9)	0.0001
Uncomfortable at social gatherings?	64.31 (23.8)	74.22 (23.9)	0.0022	48.89 (32.6)	68.92 (31.6)	0.0003
Uncomfortable in exchanges of affection?	61.40 (34.0)	73.86 (28.0)	0.0045	50.14 (34.1)	69.67 (32.2)	0.0002
Bothered by time spent removing hair?	59.4 (32.6)	69.57 (29.2)	0.0182	46.94 (33.1)	68.53 (31.1)	0.0001

Based on an analog scale of 0-100

The difference between the treatment groups for the reduction of the score for different questions varied between approximately 9 and 11 units in DE 140-001 and between 19 and 21 points in DE 140-002. Differences between treatment groups were no longer statistically significant 8 weeks after cessation of therapy.

For the other secondary endpoint, video image data, the results of the analysis for DE 140-001 and DE 140-002 at the end of treatment demonstrated no statistically significant treatment difference for the evaluation of hair growth (success defined as hair length reduced by at least 50%). Of the subjects treated with eflornithine cream in study DE 140-001, 6.3% were deemed successes (at least 50% reduction) compared with 1.3% for those treated with the vehicle. In DE 140-002 8.6% of the subjects

treated with eflornithine cream were deemed successes compared with 2.6% for those treated with the vehicle.

For the spatial mass, the results demonstrated a statistically significant treatment difference in favour of eflornithine. At the end of treatment in DE 140-001, the mean spatial mass for the eflornithine-treated subjects was 0.037 mm^2 and 0.046 mm^2 for the vehicle-treated subjects (p=0.0001). At the same time point in the study DE 140-002, mean spatial mass for the eflornithine-treated subjects was 0.036 mm^2 and 0.043 mm^2 for the vehicle-treated subjects (p=0.0004).

Clinical studies in special populations

No clinical studies have been performed in special populations.

Supportive studies

GMEH-2664

A Phase II open-label study, which was conducted using prototype formulations of eflornithine.

GMEH-2664 was the first study of women with hirsutism. It was an open, multi-centre study where thirty subjects were enrolled and 24 completed the treatment twice daily for 24 weeks with eflornithine 15% (equivalent to 3.83, 7.67 and 11.5% anhydrous hydrochloride free) cream and 12-week post treatment follow-up. It was concluded at the end of study that all subjects, except two, experienced a reduction in the number of hairs in the treated area. However, although individual data have been provided, no formal efficacy results are available and conclusions with respect to efficacy are not possible.

DE140-010 and DE140-011

These open-label non-comparative studies were of similar design, however, DE140-010 had a 12-month treatment period, whereas DE140-011 had a 6-month treatment period. Inclusion criteria included 20 hairs on the chin and upper lip and twice weekly removal of facial hairs. The PGA was the primary efficacy measure.

In DE140-010, ten US investigators enrolled 216 subjects; 144 subjects completed the 52-week treatment phase and 142 completed the study (including 4-week follow-up). At 20 weeks, 18.4% (32/174) of subjects were rated as clear/almost clear or markedly improved on PGA and at 52 weeks, 23.9% (35/146) were considered responders (clear/almost clear or markedly improved). For 80.7% of the subjects improvement or greater response was demonstrated. Improvement increases slightly from week 20 to 52 and the study implies that there is a continuous effect as measured by PGA. A total of 34% of subjects discontinued the study, in majority of cases due to subjects 'lost to follow-up'.

In DE140-011 754 subjects were enrolled by 31 investigators from multinational sites, 612 completed the 26-week treatment phase and 577 completed the study (including 4-week follow-up). At 26 weeks, 47.3% (289/611) were rated clear/almost clear or markedly improved as determined by PGA. For 90.3% of the subjects improvement or a greater response was demonstrated. A total of 23% of subjects discontinued the study in the majority of cases due to subjects 'lost to follow-up'.

Discussion on clinical efficacy

The primary efficacy endpoint is the Physician's Global Assessment (PGA). The results from the two pivotal studies demonstrate a treatment effect evaluated as successful outcome of 24.4% - 43.9% versus 4.3% - 12.9% of the study population for eflornithine and vehicle respectively. This would mean an approximate percentage points difference of 20-31 for subjects evaluated as successful outcome as compared with the vehicle. It was, however, not obvious from the submitted documentation how the physician's initial pre-treatment evaluation at baseline was performed or how the investigator graded the extent of facial hirsutism in relation to further assessment of the PGA. In response to the List of Questions the applicant stated that the clinical criterion for entry to the studies was a diagnosis of facial hirsutism made following visual inspection of subjects by trained investigators. Other criteria for eligibility included a requirement that subjects were regularly removing hairs two or more times a week, video analysis quantifying hair count on the upper lip and chin/neck, and a significant level of bother on Subject Self-Assessment Questionnaires (SSAQ).

About 60% of patients reported baseline levels of bother/discomfort in excess of 90/100 (i.e., on the last tenth part of the visual analogue scale) on the SSAQ, in both pivotal studies, and on both arms of these studies. In both pivotal studies, distributions at baseline of the video analysis results were similar between treatment arms, except for hair length in Study DE140-002, which had a statistically significant baseline treatment difference (p=0.011) with the vehicle mean (0.497 mm) slightly lower than the active (0.535 mm). Baseline differences were corrected for in the analysis presented. The baseline data from the secondary efficacy criteria (video image analysis and SSAQ), therefore, indicate that patients entering the study had a significant severity of facial hirsutism.

Only subjects in the first two categories of the PGA (clear/most clear or marked improvement) were considered as successes. However, in response to the List of Questions the applicant submitted the results based on the definition of success as clear/almost clear, marked improvement and improvement. The results show that the magnitude of differences in response rates are similar for both analyses as the response rates, for both pivotal studies pooled, when 'improved' is considered as success are 70% for eflornithine and 41% for vehicle and 35% for eflornithine versus 9% for vehicle, when improved is considered as failure.

To further validate the PGA the relationship between the several endpoints (PGA, hair length, hair mass, SSAQs) regardless of treatment and group was determined and provided in response to the List of Questions. A consistency in the response and the incremental response over time including worsening at 8 weeks after stopping treatment at 24 weeks was seen. Moreover, the changes in the video analysis data (hair length and hair mass respectively) and SSAQ were parallel to improvement or lack of improvement of the PGA. Greater PGA responders clearly demonstrated stronger responses in objective measures of length and area change with treatment. These length and area changes were consistent for both pivotal trials. Patients' responses to the SSAQ also correlated with PGA score as groups with greater levels of PGA improvement also showed greater levels of SSAQ response.

Analysis of prognostic factors, such as effects of age, race and prior hair removal technique upon the primary response measure, demonstrated an effect of race only. The response rates for DE140-001 were 30.6% and 13.3% for Caucasian and Black subjects, respectively. In Study DE140-002 the response rates between Caucasians and Black subjects were more similar with 46.2% and 35.2%, respectively rated as successes. The difference in success rates is reflected in the SPC. The difference in effect size (active treatment versus placebo) between normal-weight and over-weight women increases over time indicating a less pronounced effect in obese women. This is reflected in the SPC.

In the proposed SPC it states that 27% of non-white women and 39% of white women showed a marked or better improvement whereas the US labelling refers to success rates of 22% and 37% in non-whites and whites, respectively. In answer to the List of Outstanding Issues the applicant explained that the clinical datasets are identical but the calculation of the success rate is different. In the centralised application data include all subjects withdrawing during the treatment period with their last PGA observation carried forward. The figures in the US labelling are, however, calculated assigning the subjects without a PGA measurement at week 24 as treatment failures. A statement indicating that the data provided include all subjects with their last PGA observation carried forward to the end of treatment) was therefore included in the SPC, to explain the difference in the figures in the US labelling and the SPC.

Subjects who rated the level of bother as greater than or equal to 20 mm (analog scale 0-100 mm) were included in study. However, the magnitude of fall in 'level of bother' which could be considered clinically significant was not prospectively defined.

It can be anticipated that in practice physicians will differ in their clinical impression of degree of improvement. However, it is the patient's impression of the therapeutic benefit that is most relevant. The Self-assessment questions were generally directed at the psychological and social aspects of facial hirsutism. In determining the efficacy of eflornithine it could have been more valuable to know whether the subjects were satisfied with the magnitude of the effect, effects on hair characteristics, and whether they would continue treatment. However, the quality of life assessments were not designed to evaluate behaviours such as hair removal in a quantitative sense, but rather they were designed to elicit qualitative impressions associated with the 'condition'. The bother scales of the SSAQ do not measure behaviours associated with hirsutism, but rather how upset are the patients with their specific condition and how they interpret interference with aspects of daily life.

In response to the List of Questions the applicant submitted further analyses comparing SSAQ results to the primary endpoint, PGA, in order to further evaluate the relevance of the SSAQ findings. There is a very good concordance of SSAQ with the PGA over the study period including the four week no treatment phase at the end of the study during which both PGA and SSAQ deteriorate in parallel. Similar concordance was observed when each of the individual questions of the SSAQ was compared to the PGA response.

Pooled data showed that at baselinefor both the eflornithine 15% (equivalent to 3.83, 7.67 and 11.5% anhydrous hydrochloride free) cream and vehicle treated women had a mean value of 89 for general bother , indicating a high degree of distress over their condition. At the end of treatment (24 weeks) the pooled data from both trials showed a 31 point decrease in women receiving eflornithine 15% cream compared with a 14 point decrease for the vehicle treated group ($p<0.01$). Similar statistical differences in favour of eflornithine 15% (equivalent to 3.83, 7.67 and 11.5% anhydrous hydrochloride free) cream ($p<0.01$) were observed for the other five SSAQ questions. Thus, there was uniformity of results across the questions within the SSAQ in each study and across the two pivotal studies.

A responder analyses with a cumulative distribution of difference from baseline (in 10 mm intervals) for the question on 'bother by facial hair' of the SSAQ by treatment arms was presented by the applicant during the oral explanation. The difference between the treatment arms is greatest at an improvement of more than 20 points, where 53.1% of Vaniqa treated subjects showed this improvement compared to 25.4% in the vehicle group. There is a consistent separation in the SSAQ score between Vaniqa and vehicle treated subjects.

In addition when patients were grouped according to the PGA assigned to them at week 24 and analysed for SSAQ response those patients graded as most improved by the physician (PGA) indicated similar high levels of self-assessment response. This relationship holds true for all four PGA response groups with SSAQ mean data showing non-overlapping 95% confidence intervals for all time points on treatment beyond week 8. The benefits of treatment receded and were no longer significant 8 weeks after treatment cessation.

In conclusion, the above findings support a consistency of the SSAQ results.

A number of problems were encountered with the video image analysis. For example, 'data files for the video image analysis showed a many-fold excess of the expected number of hairs being identified by the software' due to 'numerous artefacts that were being counted as hairs'. As a result, many hair measurements calculated by this software could not be used and it was determined that each image would be reviewed visually to manually select hairs. In order to implement the manual selection of imaged hairs, a new software package was developed. However, the large volume of data stored on the equipment resulted in malfunctioning of the software and the loss some images and data.

In response to the List of Questions the applicant stated that, when used as an entry criterion, video image analysis might have underestimated the hair count due to contrast problems (problems identifying grey hairs on light skin, light hairs on light skin, and dark hairs on darker black skin). It is argued that this may have resulted in the disqualification of subjects who may have been eligible.

When used to measure the secondary efficacy parameter, the technique tended to overestimate the hair count as artefacts were counted as hairs, however, it appears that this would not have occurred at baseline as baseline images were reviewed for the purpose of excluding artefacts and verifying hair count. For the secondary efficacy parameter the artefacts were excluded in a blinded fashion. Because of these problems, complete image data for the baseline and final (Week 24 or early discharge) visits (the primary evaluation period), were obtained for about 70% of the subjects in the two studies. The video analysis data from this relatively smaller "core group data set" (patients with image data analyses) for the secondary efficacy measures of hair length and hair spatial mass still showed statistical superiority of active over vehicle in each of the two studies despite the reduced power. The PGA success rates for these "core groups" were also consistent with the success rates for all subjects randomised.

Clinical safety

Patient exposure

Safety data are available on 315 healthy individuals and 1,749 subjects enrolled in 12 trials. A total of 1375 subjects were exposed to eflornithine 15% (equivalent to 3.83, 7.67 and 11.5% anhydrous hydrochloride free) cream identical to the one proposed for marketing.

A total of 944 subjects with excessive facial hair received eflornithine for 24 weeks and 134 subjects received treatment for at least one year.

Although recently marketed in USA (27 July 2000), there is as yet no significant post-marketing data.

Adverse events and serious adverse events/deaths

In DE140-001 and DE140-002 more than 80% of subjects reported adverse events following exposure to either eflornithine or vehicle (regardless of relation to treatment). In DE-140-001, a total of 33% of subjects reported adverse events which were considered related to treatment; in DE 140-002, 53% of subjects reported adverse events which were considered related to treatment.

The number of patients in study DE-140-001 and DE140-002 with treatment related adverse events relating to the skin and appendages is given below.

Number (%) of Subjects with Treatment-Related Skin and Appendages Adverse Events

Studies DE 140-001 and DE140-002

	Eflornithine (N=395) n (%)	Vehicle (N=201) n (%)
Acne	84 (21.3)	43 (21.4)
Pseudofolliculitis barbae	64 (16.2)	31 (15.4)
Burning, stinging, tingling skin	56 (14.2)	10 (5.0)
Pruritis	15 (3.8)	8 (4.0)
Rash, Papular rash	8 (2.0)	0 (0.0)
Dry Skin	7 (1.8)	6 (3.0)
Alopecia	6 (1.5)	5 (2.5)
Erythema	5 (1.3)	0 (0.0)
Skin irritation	5 (1.3)	2 (1.0)
Dermatitis	4 (1.0)	1 (0.5)

With the exception of burning or stinging skin, the adverse event profile appeared similar for both groups. Vaniqa was compared to vehicle not placebo. The skin-related adverse events were generally mild in intensity. Subjects were specifically evaluated for acne and pseudofolliculitis barbae and these adverse events were the most frequently reported adverse events in both groups. Apparently an evaluation of the baseline photographs of subjects enrolled in the pivotal studies confirms the presence of these two conditions in the study population. Only subjects with severe inflammatory acne were excluded from the study. As alopecia is a known adverse event of eflornithine when administered intravenously, the subjects were specifically evaluated for alopecia. Most reports of alopecia were not considered related to treatment and for those considered related to treatment the incidences were similar.

The proportion of subjects reporting skin-related adverse events in the two treatment groups was similar across race and for hair removal methods used prior to treatment; the numbers were too small to draw any conclusions for age.

Subjects were specifically asked about adverse events, which have been associated with intravenous administration of eflornithine hydrochloride (e.g. hair loss, facial swelling, seizures, hearing impairment, stomach upset, loss of appetite, headaches, weakness and dizziness). The number of subjects reporting systemic symptoms related to treatment was very low and did not differ between groups. In addition, haematological parameters (thrombocyte count, leukocyte count and liver enzymes) were specifically monitored. There were few haematological abnormalities reported and most were considered unrelated to treatment.

In study DE140-001 and DE140-002 eleven eflornithine-treated subjects and six vehicle-treated subjects discontinued due to adverse events. In study DE140-010 and DE140-011 only 1% and 2% respectively of subjects discontinued due to treatment-related adverse events. In DE140-001 and DE140-002 six patients treated with eflornithine and four patients treated with vehicle required dose reduction or interruption due to adverse events.

In DE140-010 and DE140-011 42% and 30% respectively had adverse events considered related to treatment. Most of these subjects (34% in DE140-010 and 24% in DE140-011) had treatment-related adverse events which occurred on the skin. These were usually considered mild. The most frequently reported adverse events in DE140-010 were dry skin (7.4%), acne (6.9%), alopecia (6.5%) and pruritus (5.1%) and in DE140-011 acne (6.6%) and alopecia (4.8%); folliculitis was reported by 1.5% of subjects.

In GMEH 3071, the dose-finding study, 125 subjects reported 473 adverse events. The adverse events associated with the skin were reported most frequently. Acne was reported in 34 events and application site reactions in 34 events. The incidence of acne did not appear to be associated with increasing concentration of eflornithine, whereas stinging appeared to be dose-related. The majority of adverse events were determined to be mild in intensity.

In GMEH-2664 only one adverse event was reported. The adverse event (vaginal bleeding) was considered to be unrelated to treatment.

Serious events were reported in 82 of the 2064 subjects (4%). These are summarised below.

Number (%) of Subjects with Serious Adverse Events

Study	Eflornithine Drug Relationship		Vehicle Drug Relationship	
	No n (%)	Yes n (%)	No n (%)	Yes n (%)
GMEH-3071	3 (3)	0 (0)	2 (2)	0 (0)
DE140-001	12 (6)	0 (0)	2 (2)	0 (0)
DE140-002	9 (4)	0 (0)	3 (3)	0 (0)
DE140-010*	17 (8)	0 (0)	NA	NA
DE140-011	34 (5)	0 (0)	NA	NA
Total	75 (4)	0 (0)	7 (3)	0 (0)

* One death not included in total number of SAEs

The majority of serious adverse events were hospitalisations for diseases across many body systems. They were all considered as unrelated to the treatment and included fracture of bone, chest pain, basal cell carcinoma, depression, abdominal pain, pneumonia, uterine fibroid enlargement and vomiting.

There were three cases of basal cell carcinomas, none of which were considered related to study medication. All three subjects had received active treatment. Two had their carcinoma on areas of the skin that were not treated with the study medication. One 54-year old subject was diagnosed with a basal cell carcinoma on the right lower leg on Day 86. The subject reported that she had noticed the growth 5 months prior to enrolling in the study and she also had a history of a basal cell carcinoma on her nose. One 59-year old subject in DE140-002 was diagnosed on Day 120 with a basal cell carcinoma on her nose. There was a baseline history of carcinoma in this area. A 66-year old subject was diagnosed with a basal cell carcinoma on the left cheek on Study Day 182. The lesion was excised following completion of the study.

There were no deaths in study DE140-002, DE140-002, DE140-010 or GMEH 3071. However, in study DE140-011 there was one death considered unrelated to treatment (road traffic accident).

Eflornithine has been available as an intravenous medicinal product for several years in the EU. Adverse reactions in association with the intravenous administration have been identified and include hair loss, facial swelling, seizures, hearing impairment, stomach upset, loss of appetite, headaches, weakness, dizziness and haematological abnormalities, such as thrombocytopenia, leucopenia and altered liver function. Apart from alopecia and possibly facial swelling, these reactions have not been identified in the clinical studies of the topical administration of eflornithine 15% (equivalent to 3.83, 7.67 and 11.5% anhydrous hydrochloride free) cream.

Laboratory findings

Analyses for blood chemistry, haematology and hormones including free testosterone, prolacatin, follicle stimulating hormone (FSH), luteinizing hormone (LH), dehydroepiandrosterone (DHEA) were done within the pivotal studies. No clinically significant trend of clinical chemistry, hormonal and haematology parameters versus baseline was identified.

Safety in special populations

There were no safety studies performed in special populations.

Discussion on clinical safety

Eflornithine appeared to be well-tolerated when used for up to 52 weeks. The adverse event profile of the longterm trials was consistent with that reported in the shorter pivotal trials, however, the proportion of subjects reporting acne and folliculitis was lower and alopecia higher. Subjects in the open-label, longterm studies had, on a percentage basis, 3-4 times as many reports of alopecia that were considered related to the treatment compared with pivotal trials. It can be accepted that a reasonable explanation for the increased amount of reported alopecia in the open-label studies could be the active questioning. However, the adverse reaction is in line with the pharmacological activity of the drug and the open-label studies contain the present available long-term data. Accordingly, the frequency of reported alopecia in the safety studies is addressed in the SPC.

No photo-toxicity reactions have been reported within the clinical trials and this absence is supported by the pre-clinical and clinical phase I-II studies. Local pigmentary changes such as Berloque dermatitis could indicate an interaction with light with potentiation of melanogenesis. There are only a few reports of hyper-and hypo-pigmentation reported. Four cases of hyper-pigmentation were reported, 2 cases in both the active treatment group and vehicle-treated group in study DE140-002. The hyperpigmentation adverse events were considered by the investigators as post inflammatory and secondary to acne or pseudofolliculitis barbae and not related to treatment. Two cases of hypopigmentation were reported one in study DE140-001 and one in DE140-011. One case was considered possibly related to therapy, and one case as not related to the therapy. The two cases of hypopigmentation both resolved within the study period.

Treatment-related adverse events involved the skin in the majority of cases, however, these adverse events were usually considered mild and did not result in discontinuation from the study. The high proportion of subjects reporting acne and pseudofolliculitis barbae following exposure to eflornithine or vehicle in the pivotal studies is, however, of concern. Both conditions may cause further distress to women with excessive facial hair who are prescribed eflornithine. In response to the List of Questions the applicant submitted a further evaluation of acne and pseudofolliculitis barbae during the pivotal study periods, which do not suggest that eflornithine 15% has severe acnegenic potential. However, it should be noted that 14% of subjects in each treatment group (active or vehicle) who did not have acne and 9% of the subjects, who did not have pseudofolliculitis barbae at baseline, became worse during the treatment. For the group of subjects, who worsened during the study period, the treatment group with active cream had a slightly higher tendency for a grade two change of worsening compared with the vehicle treated group. However, the majority of subjects, whether in the active or vehicle-treated group, were unchanged in their acne grade compared with baseline.

In response to the List of Questions the results from a rabbit ear comedogenicity study was submitted. The study showed no evidence of comedogenicity from Vaniqa or vehicle cream. While there were significant and severe treatment related histological findings of comedogenicity with standard positive control (1% coal tar).

Although eflornithine in different published pre-clinical study-models appears to possess some chemopreventive effect of carcinogenesis rather than the opposite, adverse events such as skin malignancies are of concern. It is reasonable to believe that most basal cell carcinomas would need a longer exposure period than the reported study duration to develop and be detected. In white races, basal cell carcinoma is the commonest malignant tumour of the skin. A population-based incidence study in Minnesota reports an annual incidence for females of 124 per 100 000 annum while a recent Australian survey gives an incidence of $605/10^{5}$ for females. Given that the study population of the Minnesota report would reasonably reflect subjects of the pivotal studies and calculating on the basis

of the 944 subjects that were treated for 24 weeks, the corresponding figures for the study population would be approximately 106 per 100 000. In conclusion these figures do not indicate an increased risk for the treated population of developing basal cell carcinoma and the pharmacological profile of eflornithine acting as an anti-proliferative substance supports this finding. However, it should be noted that these calculations are made on the basis of a treatment period of only 24 weeks + 8 weeks of follow-up. The true incidence/ treatment year is not known.

On the other hand, the possibility of developing skin atrophy with long-term topical application of a substance interfering with cell proliferation on skin areas exposed to UV-light with an additional atrophy potential is a highly relevant issue and should be considered. Apparently no cases of skin atrophy were reported in any of the clinical trials. However, this could be an adverse event appearing after a long treatment period. A possibility of any type of rebound-phenomenon appearing after cessation of therapy after a long treatment period should also be considered. The applicant has argued that because of the inhibition of ODC being intermittent it is less likely to suppress the cells' potential to proliferate. However, the aim of the submitted documentation is to demonstrate efficacy in terms of suppression of the hair growth with a twice daily application. Although the cell turnover of the hair root is more rapid than that for the epidermis, the possible effects of longstanding intermittent suppression of the keratinocytes cannot be ignored. An increased incidence of skin atrophy was not demonstrated in the animal studies. However, in one of the studies, a two-year study in mice, there were histological findings of acanthosis of the epidermis at the end of the study. The applicant has been requested to address the question of eflornithine potentiating the atrophy in sun exposed areas of the skin as a follow up measure.

While most adverse events are reported in slightly higher percentages of subjects in the one-year study than in the six-month study, there is no individual adverse event whose frequency increases substantially. The reason for the higher percentage of subjects having treatment-related adverse events in the one year study can be attributed to the longer period of study duration.

5. Overall conclusions and benefit/risk assessment

- **Quality**

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

- **Preclinical pharmacology and toxicology**

Overall, the primary pharmacodynamic studies provided adequate evidence that eflornithine inhibits hair growth in relevant animal models.

The absorption of eflornithine is low following single dermal applications.

Overall, the toxicology programme revealed that eflornithine was not genotoxic and no tumour inducing effect was observed in the carcinogenicity studies including one photocarcinogenicity study and two oral studies in rodents at high doses relative to humans.

Eflornithine had no effect on male or female fertility. No teratogenic effects were observed in rats and rabbits at doses up to 180 and 36 times the human dose, respectively. Higher doses resulted in maternal and foetal toxicity without evidence of teratogenicity.

This information has been included in the SPC.

- **Efficacy**

A statistically significant difference of improvement in favour of eflornithine 11.5% cream over vehicle was seen during the treatment period with from week 4 onwards. Following the cessation of therapy, the effect decreased and no statistical significance versus vehicle was seen after 8 weeks.

The difference in success rates between non-whites and whites is reflected in the SPC. The difference in success rate between normal-weight and over-weight women is also reflected in the SPC.

There was a significant difference in both pivotal studies for all six questions on quality of life relating to the impact of facial hair as assessed by the subject in favour of the eflornithine-treated group compared with the vehicle group.

The most relevant parameter was considered to have been the patient's impression of the therapeutic benefit. It would therefore have been valuable to know whether the subjects were satisfied with the magnitude of the effect, effects on hair characteristics, and whether they would continue treatment. However, a concordance between the patient's self assessment and the physician's assessment was shown.

- **Safety**

The most common treatment related adverse events were acne and pseudofolliculitis barbae and burning, stinging, tingling of the skin. With the exception of burning, stinging or tingling of the skin there was no difference between the treatment groups with regard to frequency or type of adverse event in the two 24-week studies. In the two longterm studies the adverse events acne and pseudofolliculitis barbae were reported less often than in the 24-week studies.

Most of the AEs reported during the study were graded as mild to moderate in severity. Most serious events were related to hospitalisation and were all considered as unrelated to the treatment.

There were three cases of basal cell carcinomas, none of which were considered related to study medication. There was one death reported, which was considered unrelated to treatment (road traffic accident).

Evaluation of acne incidence and severity in the Vaniqa trials revealed no evidence of relation to either Vaniqa or the vehicle cream. Background (baseline) incidences of approximately 41% were observed in each of the pivotal trials and remained unchanged throughout the trials. The animal and clinical data do not suggest that Vaniqa or its vehicle precipitate acne.

An issue remains regarding the effect of eflornithine on normally replicating cells within the skin and the possibility of an increased risk of skin atrophy after long-term treatment of normal skin and enhanced skin atrophy on areas exposed to UV-light. It can be concluded from the clinical trials that no clinical signs of atrophy was reported and published studies indicate similar beneficial effects (minimise and reversal of actinic damage) for eflornithine as have been previously demonstrated for the retinoids. However, previous published studies of topical retinoids show that clinically visible changes of the skin are minimal after 3 months of treatment although transformations are evident histologically. The applicant has therefore been requested to address the question of eflornithine potentiating the atrophy in sun exposed areas of the skin as a follow up measure.

Benefit/risk assessment

During an oral explanation held during the CPMP on 15 November 2000, the applicant addressed the following issues:

1. The concern that the opinion of the patient on the success of the treatment has not been adequately addressed
2. A further responder analysis of the SSAQ results, illustrating the difference in responder rate for a range of responder definitions (cut-off points) and supporting the consistency of the SSAQ results
3. The risk of enhanced skin atrophy of sun-exposed skin areas with longterm daily application and the potential for eflornithine to precipitate or potentiate acne in the context of the overall benefit/risk assessment.

The overall benefit/risk assessment is considered to be positive considering that

- A clinically relevant effect was seen in the target population (females with facial hirsutism) and that there was a good concordance between the physician's assessment and the patient's self assessment

- The adverse reactions were mostly skin related, of mild intensity and resolved without discontinuation of Vaniqa. The most frequently reported adverse reaction was acne, however, animal and clinical data do not suggest that Vaniqa or its vehicle precipitate acne.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Vaniqa in the treatment of excessive facial hair in women was favourable and therefore recommended the granting of the marketing authorisation.