SUMMARY SHEET FOR ODAC

Drug: Histamine dihydrochloride

Applicant: Maxim Pharmaceuticals, Inc.

Indication: Histamine dihydrochloride is indicated for adjunctive use with interleukin-2 in the treatment of adult patients with advanced metastatic melanoma that has metastasized to the liver.

Study MP-US-M01 is a randomized multi-center, open-labeled study designed to demonstrate the added benefit of histamine to IL-2 in the treatment of metastatic melanoma. 305 patients were enrolled in the study. No stratifications of prognostic factors were performed and the efficacy and tolerability of the treatment regimen used in the study have never been demonstrated in a pilot study. The primary efficacy endpoint is survival. The applicant is seeking the above indication based on efficacy results in a subgroup of 129 patients with liver metastases in a single study, MP-US-M01.

The following table summarizes the FDA's analysis of efficacy and safety from study MP-US-M01:

	ITT IL-2 (N=153)	ITT H/IL-2 (N=152)	ITT-LM* IL-2 (N=74)	ITT-LM* H/IL-2 (N=55)
Survival (days)				
Median	245	272	154	283
95% CI	184-281	211 - 318	119 - 204	197 – 387
p-value	0.1255		0.0040	
Response Rate	3%	3%	0%	4%
Time to progression	Pending	Pending	Pending	Pending
Withdrawal**	143	140	71	51
Death	3	3	**0**	**2**
Progression	109	110	56	38
AE	20	16	10	6
Death within 28 days of study med	13 (8%)	17 (11%)	8 (11%)	10 (**18%**)
Grade 4 toxicity	8 (5%)	10 (7%)	1 (1%)	4 (7%)
Grade 3 toxicity	90 (59%)	79 (52%)	49 (66%)	31 (56%)

*Patients with liver metastases at study entry

**Reasons for withdrawal as per the applicant

Metastatic melanoma is known to have a variable clinical course influenced by prognostic factors. FDA analysis of the distribution of known prognostic factors in metastatic melanoma found many imbalances between the two treatment arms in patients with liver metastases. These included performance status, albumin, disease-free interval, and number of metastatic sites. These imbalances consistently favored the histamine/IL-2 arm. This raises a concern that the apparent survival difference in this subgroup may be attributed to patient selection and the natural history of the disease.

FDA safety review found that the death rate within 28 days of the last dose of study medication was as high as 18% in the 55 patients with liver metastases who received the combination of histamine/IL-2. The incidence of grade 3-4 toxicities is 58% in the entire study population (N=305) and 62% in patients with liver metastases (N=129). In the absence of a control arm with no IL-2, it is not possible to determine how many of these deaths and grade 3-4 toxicities are due to the underlying disease. In the recently published randomized trial of temozolomide versus dacarbazine (N=305), the percentage of patients reporting grade 3 or 4 adverse events was 36-38% and 24 deaths occurred during treatment (8%). The applicant did not perform an analysis of dose reduction and treatment delays.

Issues for discussion at ODAC: The proposed indication of histamine plus IL-2 is for patients with melanoma metastasized to liver.

1) In the subgroup of patients with liver metastases, there are many imbalances in prognostic factors between the two treatment arms. Does the apparent survival difference in this subgroup of patients from a single trial represent persuasive evidence of treatment efficacy?

2) The administration of this IL-2 regimen with or without histamine is associated with significant toxicities. The incidence of grade 3-4 toxicities is 58% in the entire study population (N=305) and 62% in patients with liver metastases (N=129). Among the 129 patients with liver metastases at study entry, 18 died within 28 days of the last dose of study medication. Given the observed toxicity data, is this treatment a safe and tolerable regimen in patients with liver metastases?

MEDICAL OFFICER PRELIMINARY REVIEW OF NDA#21-240

Drug Name: Histamine Dihydrochloride
Applicant: Maxim Pharmaceuticals, Inc.
8899 University Center Lane, Suite 400
San Diego, CA 92122
Related INDs: #[ ]
Date submitted: July 18, 2000
Date of review: November 15, 2000

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1. General Information

Drug Name:	Histamine Dihydrochloride
Applicant:	Maxim Pharmaceuticals, Inc.
NDA Submission Date:	July 18, 2000
Pharmacologic Category:	Immune modulator
Proposed Indication:	Treatment of metastatic melanoma to liver
21-Day Filing Meeting:	Priority Review
FDA request for information	October 19, 2000
FDA request for information	November 8, 2000

1.1. Drug name and chemical characteristics

The following information was obtained from NDA desk copy Vol. 2.1 and the labeling.

1.1.1. Generic /USAN name

Histamine dihydrochloride

1.1.2. Trade name

Pending

1.1.3. Other names

Torcan D586

1.1.4. Chemical name

1*H*-imidazole-4-ethanamine dihydrochloride

1.1.5. Structural formula

The molecular formula is $C_5H_9N_3 \bullet 2HCl$ and the molecular weight is 184.07.

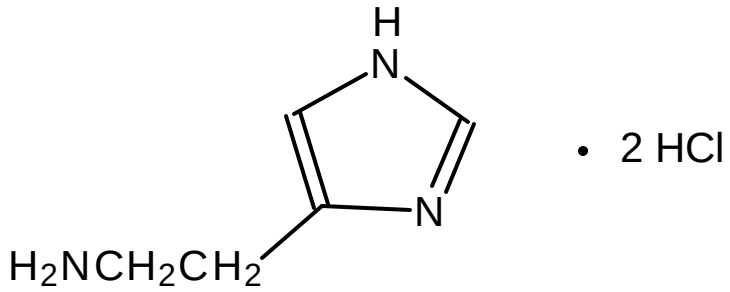

Figure 1: Chemical Structure of histamine dihydrochloride

1.1.5. Formulation

Histamine Dihydrochloride Injection is supplied as a clear sterile liquid in 1 mL single dose vials and 10 mL multi-dose vials. Each mL in the single dose vial contains 1 mg of histamine dihydrochloride, 8.6 mg of Sodium Chloride, USP in Water for Injection, USP. Each ml in the multi-dose vials contains 1 mg of histamine dihydrochloride, 8.6 mg of Sodium

Chloride, USP and 9.0 mg Benzyl Alcohol, NF (preservative) in Water for Injection, USP.

The pH of both injectable solutions is 3.5 to 5.5. The final concentration of histamine base in this formulation is approximately equivalent to 0.6 mg histamine per mL.

1.1.6. Foreign marketing experience

Histamine has not been approved for marketing in any country for the proposed indication nor has it been withdrawn or suspended from marketing in any country for the proposed indication.

1.1.7. Pharmacologic category

Immune modulator

1.1.8. Proposed indication

Histamine dihydrochloride is indicated for adjunctive use with interleukin-2 in the treatment of adult patients with advanced metastatic melanoma that has metastasized to the liver.

1.1.9. Dosage form(s) and route (s) of administration

Histamine Dihydrochloride Injection, 1 mg/mL, should be administered by slow, controlled subcutaneous injection at a rate not to exceed 0.1 mg per minute (i.e., 1 mg over 10 minutes), about 5 to 10 minutes after the administration of IL-2 has been completed. The rate of infusion may be lengthened to 20 minutes (0.05 mg per minute) to eliminate or reduce side effects but should not exceed 30 minutes. Patients should remain sitting or supine for approximately 30 minutes after the completion of the injection.

Drug	Dose and Regimen
Interleukin-2	9.0 MIU/m^2, SC , BID, days 1 and 2 of weeks 1 and 3 2.0 MIU/m^2, SC , BID, days 1 through 5 of weeks 2 and 4
Histamine	1 mg, SC , BID, days 1 through 5 of weeks 1 through 4

1.1.10. Related drug(s)

None

1.1.11. Financial Disclosure

A total of sixty-three investigators did not fill out the Financial disclosure forms, and four investigators (Drs. Peter Boasberg, Rene Gonzales, Steven O'Day, and Steven Tucker) received significant payment from the applicant in the form of a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria. All four investigators participated in the major trial of MP-US-M01, except Dr. Steven Tucker who only participated in MP-MA-0103.

2. Regulatory History

This part of the review is a summary of the correspondence between the Applicant (sponsor) and FDA, as well as meeting minutes.

February 4, 1997: The sponsor submitted IND #[ ], which contained the protocol of a phase III trial without justification for the proposed dose and schedule of IL-2 or histamine. There were no phase I/II data to support the safety and efficacy of the proposed dose and schedule of IL-2 and histamine. DODP informed the sponsor that the proposed study could not proceed until relevant data was submitted and reviewed by FDA.

[ ].

April 9, 1997: DODP met with the sponsor to provide guidance on the development of histamine/IL-2 combination for metastatic melanoma. 1) DODP recommended that a small pilot trial be performed to test the tolerability and feasibility of the proposed dose and schedule of histamine/IL-2. The sponsor stated that they would take a risk by not doing a pilot trial first. DODP recommended a reduction of the proposed IL-2 dose because almost all patients in the most recent Swedish trial required dose reduction by cycle 3. The sponsor stated that the chosen dose of IL-2 was consistent with what was being used by clinicians and they would like to proceed with the full dose as proposed. 2) DODP pointed out that the phase I/II Swedish trials did not provide sufficient data to support median survival estimates, which were essential for sample size calculations. 3) The Agency's requirement of at least two adequate and well-controlled trials for approval

of a drug was discussed. DODP stated that the added benefit of histamine to IL-2 should be demonstrated in studies sufficiently powered to show substantial superiority of the histamine/IL-2 arm over IL-2 alone. **The arms should be balanced in terms of known prognostic factors and DODP recommended that the sponsor perform pre-stratification based on the presence or absence of liver metastases.** DODP stated that a phase IV commitment could not serve as a second adequate and well-controlled trial, but a concurrent non-US protocol using histamine/IL-2 could serve as a second adequate and well-controlled trial if it used the same regime as in the US trial. A second trial designed with a different control arm such as DTIC would be risky because such a design could not isolate the added benefit of histamine to IL-2. The superiority of histamine/IL-2 over DTIC would not support NDA approval unless the first trial provided evidence that histamine added benefit to IL-2. The sponsor hoped that the results from the proposed US trial would be so compelling that a second trial would not be needed. 4) Both the sponsor and DODP agreed that survival would be the primary endpoint.

April 22, 1997: A clinical deficiency list containing 34 items was faxed to the sponsor. DODP again recommended that a pilot study be performed to document the feasibility and tolerability of the proposed dose and schedule of IL-2 and histamine or that drug doses be optimized in a small number of patients prior to full-scale enrollment. **DODP re-emphasized that all measurable lesions meeting the minimum dimension criteria should be included in the calculation of response rate.** DODP recommended that stratification be performed prospectively for key prognostic variables, such as the location and number of disease sites and prior treatment with DTIC. Pre-stratification would ensure that the study arms were properly balanced in patient characteristics that might affect survival. To demonstrate the efficacy of histamine as an immune adjuvant to IL-2, two well-controlled studies would be required, each sufficiently powered to show superiority for the histamine/IL-2 combination over IL-2 alone.

April 23, 1997: The sponsor responded to DODP comments and the list of deficiencies by stating that they would proceed with the proposed dose and schedule of IL-2 and histamine without any alterations. Regarding the stratification recommendation, the sponsor decided NOT to prestratify by liver metastasis and prior DTIC treatment but would perform subgroup analyses based on the presence or absence of liver metastases and prior exposure to DTIC.

July 23, 1997: The revised protocol of MP-US-M01 dated 7/1/97 stated patients with "clinically insignificant" progression of disease (i.e., changes in sentinel lesions not associated with a decrease in WHO status by 1 or Karnofsky status of 20 points during the first 4 cycles of treatment) would remain on study for an addition 6 weeks and be re-evaluated. The re-evaluation would not be compared to baseline measurements but would be compared to the previous evaluation at week 12. For patients with progression of disease following 3-4 cycles of treatment, the investigator may remove the patient from study at his/her discretion. FDA stated that patients with equivocal progression of disease by imaging studies at week 12 may receive another cycle of therapy, however, repeat imaging studies after the additional cycle of therapy (i.e., at week 18) should be compared to studies performed at baseline or at tumor size nadir. Patients should be removed from the study for progression of disease regardless of whether tumor-related symptoms were present or not.

September 12, 1997: FDA re-emphasized that patients with ≥25% increase in all measurable lesions at week 18 compared to imaging studies at week 12 should be considered to have unequivocal progression of disease and should be removed from the study regardless of whether tumor-related symptoms were present or not. For the purpose of statistical analysis, these patients should be considered treatment failures at week 18. There was no literature to support the sponsor's contention that continuing a treatment in patients with clinically asymptomatic progression of disease would prolong their survival. Patients should not be exposed to treatment related toxicities of an ineffective therapy.

January 8, 1998: FDA commented on study MP-MA-0102 (a phase III study in advanced melanoma to be done in Europe and Australia) which differed from the regimen used in the US study MP-US-M01 in that it combined low-dose IL-2 and α-interferon:

- FDA anticipated that the results from the US study, MP-US-M01 alone would not be sufficiently compelling for filing an NDA.
- The European study as proposed would not be considered supportive for the US study. An acceptable design for a supportive study would be: Histamine/IL-2 vs. DTIC or Histamine/IL-2/α-interferon vs. IL-2/α-interferon
- **The lack of stratification could cause imbalances. If the imbalances appeared to account for differences in the findings, the results would be questionable. Stratification of studies using the most appropriate factors was preferred e.g., liver metastases or not, prior chemotherapy or not. If subgroup analyses were planned, they should be considered exploratory,**

unless the subgroups were powered in size to demonstrate prespecified differences in survival.

January 19, 1998: The sponsor requested that histamine be designated a Fast Track Product for its use as adjunct therapy with IL-2 in the treatment of advanced malignant melanoma. The sponsor stated that the design of MP-MA-0102 reflected how malignant melanoma was treated in Sweden and Australia. The sponsor believed that the US study, MP-US-M01, would be the one adequate and well-controlled study in a US population, and the Swedish/Australian study, MP-MA-0102, would provide confirmatory evidence of efficacy. The sponsor clarified that patients in study MP-MA-0102 would be stratified by the presence or absence of liver metastases and they believed that there would be enough patients with liver metastases to detect, with 80% power, a minimum 3-fold increase in median survival time (4 to 12 months) using a two-sided log-rank test at the 5% significance level and assuming a 12-month follow-up period.

February 6, 1998: Dr. Delap wrote to the sponsor to clarify DODP's position on the two proposed studies in metastatic melanoma. Dr. Delap reiterated that DODP was not convinced that the results of MP-US-M01 alone would prove to be sufficiently positive and "compelling" to support a claim that histamine plus IL-2 were superior to IL-2 alone. DODP was interested in the design of additional studies that might be submitted as supportive evidence, in the event that the results of MP-US-M01 were weak. Dr. Delap stated that it would be impossible to isolate the added benefit of histamine in MP-MA-0102, because the experimental arm evaluated a different dose and schedule of IL-2 and added interferon, making the value of this study as a supportive study questionable. There was additional risk using DTIC in the control arm from a regulatory standpoint. If the US study showed only marginal benefit of histamine/IL-2 over its IL-2 control arm, the use of a different control arm in MP-MA-0102 might further weaken the planned NDA. Dr. Delap asked again whether the sponsor planned to carry out stratification prospectively in the US trial.

April 17, 1998: The sponsor's request for Fast Track Designation for histamine was denied by DODP.

May 5, 1998: End-of-phase 2 meeting was held to discuss what might constitute an approvable NDA for histamine for the indication of "adjuvant to IL-2 for the treatment of advanced stage malignant melanoma" and to discuss the information needed for Fast Track Designation of histamine for this indication. DODP stated that the design of MP-US-M01 was appropriate to demonstrate the added benefit of histamine to IL-2 therapy. In general, two well-controlled studies using similar dose and schedule of histamine/IL-2 would be required for approval of an indication. For each study, the two arms

should be well balanced in terms of prognostic factors. Less support from other studies might be needed if results from MP-US-M01 were compelling. DODP reiterated that the International Melanoma Study (MP-MA-0102) could not serve as a second well-controlled study. The sponsor stated that the European regulatory Committees would not allow IL-2/α-interferon as a control arm. The sponsor asked whether they could present an interim analysis of the International Melanoma Study as part of the NDA. DODP replied that FDA would want this information submitted with the NDA but the International Melanoma Study as designed was not likely to support the US Melanoma study unless the results were very strong. The sponsor asked what type of results would be considered "compelling". DODP replied that a 50% increase in median survival in the arm of histamine/IL-2 over IL-2 alone might be compelling. The arms should be well balanced in terms of prognostic factors. FDA would also look at other efficacy findings for consistent strong results and toxicity. The sponsor asked whether better quality of life would support an overall benefit for histamine. DODP replied that clinically meaningful improvement in quality of life should be prospectively defined in the protocol. The sponsor should provide data confirming the validity of the QOL questionnaire/instrument to be used in this disease setting. DODP advised that a small subset of questions with the most relevant components of QOL (particularly those related to tumor symptoms) be prospectively identified.

December 4, 1998: The sponsor submitted a new protocol for a multi-center, open-label, single-arm study to evaluate the safety and efficacy of histamine/IL-2 combination in patients with advanced melanoma. DODP communicated the following comments to the sponsor: Although this single arm study might help to substantiate the efficacy and safety of the histamine/IL-2 regimen in advanced melanoma patients, it would not directly address whether use of histamine added benefit to IL-2 in this setting without a control arm. In open-label trials, objective tumor response rate and response duration are efficacy endpoints that can be most reliably measured. Time to disease progression and survival should be evaluated but are outcomes difficult to interpret in the absence of a control arm.

October 20, 1999: Pre-NDA meeting was held. The sponsor asserted that the NDA should be approvable if substantial evidence of efficacy, i.e., $p<0.05$ was shown in the US Phase III trial in the ITT population or any of ITT subgroup for the primary endpoint. DODP stated that only study MP-US-M01 was designed to provide evidence that histamine contributed to the efficacy of IL-2, and to serve as the sole basis of approval, and it would need to provide compelling evidence of safety and efficacy. **A statistically significant survival advantage in a single subgroup would not lead to approval.** Subgroup analyses would need to be adjusted for multiple comparisons. DODP

advised that: 1) the efficacy cut-off point should be based on having a sufficient number of deaths as specified in the protocol rather than a date; 2) response should be defined by CR or PR only; 3) time to tumor progression should replace time to treatment failure as the secondary endpoint. DODP requested that the sponsor provide narratives on all patients who died on study or within 30 days of the last dose of study medications, on all of patients who suffered a serious adverse event and those previously specified in the meeting package of 9/14/99. The sponsor stated that a 4 month safety update would be submitted in November 2000 based on a July 2000 NDA submission. The cut-off date for this safety update would be August 2000. The sponsor asserted that the NDA should be approvable if the Interim Analysis of the Melanoma Scientific study (phase II trial in US) supported the findings in MP-US-M01. DODP replied that the Melanoma Scientific study could only provide safety data and would not impact efficacy claims. The Swedish studies MM-1, MM-2 and MM-3 could not support the US study, because the combination of drugs in these studies was different from the one used in MP-US-M01.

November 24, 1999: **The sponsor submitted a revised statistical analysis plan that proposed a survival analysis of the ITT population (all patients randomized) and those with liver metastases at baseline using Log Rank test. Type I error would be adjusted using the Holm-Sidak step-down procedure.**

December 17, 1999: FDA statistician deemed the statistical analysis plan for the protocol acceptable.

February 1, 2000: Histamine dihydrochloride was designated an orphan drug.

February 2, 2000: Teleconference was held to discuss the revised statistical plan and biopharmaceutical issues. The sponsor proposed to use the initial date of confirmed progression or the date the patient withdrew from the study as the date of progression. DODP stated that for time to progression calculation, deaths due to disease might be counted as progression if adequate documentation of progression was provided. Otherwise, such patients should be censored at the time of death. DODP requested that the sponsor provide information on post-treatment therapy received after tumor progression in MP-US-M01, especially biological agents. The sponsor replied that these data were not collected.

February 23, 2000: The sponsor asked whether submission of case report forms (CRFs) required by §314.50(f)(2) could be waived by the DODP.

April 24, 2000: Teleconference was held to discuss the submission of CRFs. The sponsor stated that in MP-US-M01, 11 patients died during treatment, 129 patients died within 28 days of receiving the last dose of study medication and 94 patients died >29 days after receiving the last dose of study medication as of the cut-off date of March 8, 2000. The sponsor reported that 283 patients did not complete 8 cycles of treatment and 45 patients did not complete the assigned treatment due to an adverse event. DODP requested that CRFs on all patients who died within 28 days of the last dose of study medication and those who withdrew from the study due to adverse events in MP-US-M01 be submitted in the NDA.

May 17, 2000: FDA statistician's comment on the sponsor's analysis plan of quality of life data was sent to the sponsor.

3. Manufacturing Controls

See CMC review by Dr. Nallaperumal Chidambaram.

4. Pharmacology

4.1. Overview

This section is a summary from NDA Desk copy Vol. 2.1 and the label. For details see pharm/tox review by Dr. John Leighton.

Histamine dihydrochloride is structurally related to histamine, which is normally present in human mast cells and basophils. Hellstrand K et al showed that histamine dihydrochloride inhibited the generation of reactive oxygen metabolites (ROM) from phagocytes by binding to the histamine receptors of the H2 subtype (1). *In vitro* and *in vivo* studies have shown that ROMs produced by phagocytic cells found in and around tumors irreversibly suppress natural killer (NK) cell and T cell activation, and can cause apoptosis of NK and T cells. Inhibition of the phagocyte-derived ROMs may allow for more effective stimulation and activation of NK cells and T cells by interleukin-2 (IL-2). In support of this theory, preclinical models using murine B16 melanoma showed a significant decrease in the volume of metastatic and primary lesions when histamine dihydrochloride was administered alone or in combination with IL-2 or interferon alpha. The effect exerted by histamine alone was dose-dependent in the range of 25mg/kg to 250mg/kg.

Reviewer's comments:

It appears that histamine alone at a dose of 25 mg/kg or 250 mg/kg is effective in reducing metastatic and primary lesions in animals. The additive effect from IL-2 is modest at best.

4.2. Toxicology

See pharm/tox review by Dr. Leighton for full discussion.

The following section on toxicology studies is a summary from the relevant sections in NDA desk copy Vol 2.1.

The maximum tolerated dose of histamine dihydrochloride in rats is 5000 times the proposed human clinical dose; in rabbits and dogs it is 350 times the proposed human clinical dose. Multiple dose studies revealed no differences between male and female rats in response to histamine dihydrochloride, no accumulation of histamine, and no change in pharmacokinetics over the course of these studies. Developmental toxicity studies in rats and rabbits showed no evidence of histamine related fetal abnormalities. No mutations were observed in the three standard mutagenicity assays.

4.3. Pharmacokinetics

See Dr. Williams' review for details. The following is a summary from the label.

The plasma concentrations of histamine reflected a fairly large inter-subject variation in both healthy volunteers and patients with metastatic melanoma. In healthy adults, histamine exhibited an elimination half-life of **6.8 to 20.2 minutes (mean 11.5 minutes)** following a 1 mg subcutaneous infusion over 10 minutes. The peak serum concentration ranged from 14.9 to 60.2 nmol/L (mean 38.2 nmol/L) at a mean time to peak of 17.9 minutes. There was no marked difference between men and women in the measured histamine concentrations or the calculated pharmacokinetics parameters.

The pharmacokinetics of histamine after single 1 mg subcutaneous injections over 20 minutes in patients with metastatic melanoma were similar to those found in healthy volunteers after taking into account the 20 minute infusion time. The elimination half-life ranged from 13.8 to 24.9 minutes (mean 18.1 minutes). The peak serum concentration in patients ranged from 24.7 to 89.1 nmol/L (mean 46.2 nmol/L) at a mean time to peak of 27.5 minutes. The plasma concentrations and calculated pharmacokinetic parameters were

similar in males and females. Pharmacokinetic parameters are summarized in Table 1 for both adult volunteers and patients.

Table 1. Pharmacokinetic Parameters of Histamine in Healthy Adult Volunteers and Patients with Advanced Metastatic Melanoma Receiving a Single 1 mg Subcutaneous Injection of Histamine Dihydrochloride.

Parameter	Healthy Adult Volunteers[a] (N = 21) (Mean ± SD)	Patients[b] (N = 12) (Mean ± SD)
C_{max} (nmol/L)	**38.2 (± 12.6)**	**46.2 (± 17.7)**
t_{max} (min)	**17.9 (± 4.8)**	**27.5 (± 5.6)**
$t_{½}$ (min)	**11.5 (± 3.3)**	**18.1 (± 3.5)**
V_d (L)	**49.4**	**42.3**

[a] Histamine Dihydrochloride administered over 10 minutes
[b] Histamine Dihydrochloride administered over 20 minutes

There is no pharmacokinetic information in pediatric or geriatric patients, in patients with hepatic or renal impairment, or on racial differences in pharmacokinetic parameters.

Following an intradermal dose, 4-8% of the dose is excreted in the urine as N-methyl-histamine, 42-47% as N-methyl imidazole acetic acid, 9-11% as imidazole acetic acid, 16-23% as imidazole acetic acid riboside and 2-3% as free histamine. After rapid diffusion into body tissues, histamine is almost entirely metabolized. The metabolism of histamine has been investigated *in vivo* using ^{14}C-histamine and measuring levels of the major metabolites in plasma and urine. Approximately 50% of a dose is metabolized by the enzyme histamine N-methyltransferase to N-methyl imidazole acetic acid and N-methyl-histamine. The remainder is oxidized by the enzyme diamine oxidase (DAO) to imidazole acetic acid and its riboside. Adequate pathways in tissues such as the liver, lung, GI tract, kidney and skin exist in humans to metabolize endogenously generated histamine and histamine consumed from exogenous sources (food, beverage). It is unlikely that exogenously administered histamine could saturate these endogenous metabolic pathways.

Reviewer's comment:
According Dr. Gene Williams, the Immunotech Histamine RIA assay used by the applicant to measure histamine in plasma samples cross reacts with histamine metabolites and may not have sufficient specificity to provide accurate pharmacokinetic information of histamine. The applicant did not perform pharmacodynamic analyses to explore the relationship between concomitant medications, laboratory values (e.g., albumin, creatinine clearance, liver enzymes) and the pharmacokinetic parameters. No regression

analysis was provided to look for the relationship between efficacy-related endpoints and systemic exposure as measured by volume of distribution and total clearance.

5. Clinical Background

Interleukin-2 (IL-2) is a lymphocyte derived cytokine produced by a genetically engineered E.Coli strain containing an analog of the human IL-2 gene. The recombinant IL-2 binds to a specific, high-affinity cell surface receptor expressed on activated T-cells and certain malignant lymphocytes, resulting in the activation/proliferation of cytotoxic lymphoid cell populations. Both cytotoxic T-lymphocytes and natural killer cells (NK-cells) are activated in the presence of IL-2 (1). The subsequent production of a spectrum of "secondary" cytokines by the activated lymphocytes is central to the pathophysiology of IL-2 toxicity.

Preclinical models suggest that the IL-2 antitumor activity is dose- and schedule-related. The IL-2 antitumor activity is impaired in animals whose immune systems are defective, either genetically or because of prior chemotherapy, irradiation, or the use of steroids. Hellstrand K et al (2) suggested that the suboptimal results with IL-2 and/or IFN-a therapy in humans might be due to inhibition of NK-cell activity by reactive oxygen metabolites (ROM) released by the phagocytes present at the site of the tumor. This impairment can be reproduced in vitro by mixing monocytes and NK-cells in tissue culture, where the monocytes are able to prevent lymphokine induced activation of NK-cells. Histamine dihydrochloride inhibits the generation of ROM from phagocytes by binding to the histamine receptors of the H2 subtype, eliminating the suppressive effect of ROM on NK cells.

The incidence of malignant melanoma continues to rise throughout the world. The expected risk of melanoma reaches 1 of 75 persons in 2000 (3). It is estimated that 82% to 85% of melanoma patients present with localized disease (American Joint Committee on Cancer [AJCC] stage I or II), 10% 10 13% with regional disease (AJCC stage III) and the remaining 2% to 5% with distant metastatic disease (AJCC stage IV). The median age at presentation is 45 to 50 years (4).

Among patients with localized disease, the major prognostic factors include Breslow's thickness and Clark's level, primary tumor location, the presence of tumor ulceration, and patient gender. Among patients with regional disease, tumor burden expressed as number of positive nodes, size of the largest node, and presence of extranodal soft tissue extension, seems to be

most predictive of outcome. However, among stage III patients, there are clearly subsets of patients in whom melanoma follows a very indolent natural history. With regard to metastatic disease, the New American Joint Committee on Cancer Staging system recommended incorporation of the site of metastases, the number of metastatic sites and elevated serum LDH levels in the M classification of staging because these three clinical parameters were most predictive of poor survival (5). Other prognostic factors considered but not included in the classification were performance status, disease free interval, and prior disease stage.

Melanoma is a relatively chemo-resistant disease. Prognostic information is especially important in metastatic melanoma because of its variable clinical course. **Survival in metastatic melanoma patients has been determined primarily by the extent and pace of the disease, rather than by the treatment strategy** (6) and differences or lack of differences between treatment groups may be due to imbalances of prognostic factors rather than the treatment itself (7).

Table 2 is a summary of four most frequently cited papers on prognostic factors in metastatic melanoma. **The number and site of metastatic disease referred to initial site(s) of distant metastases.** Overall survival of 1721 patients was computed from the **initial diagnosis** of metastatic disease in studies by Balch (7) and Barth (8) and overall survival of 602 patients appeared to be computed from the start of treatment on protocols (9, 10).

Table 2: Published Univariate and Multivariate Analyses of Prognostic Factors in Metastatic Melanoma

	Balch 1983 U/M*	Sirrot 1993 U/M*	Barth 1995 U/M*	Eton 1998 U/M*
Number of patients	200	284	1521	318
Preceding stage Stage I/II vs. III			**+/+**	
DFS since the initial diagnosis of primary tumor	N/Y (>12m)	Y/N (>4 yrs)	Y/Y (>18 m)	
Age	N/N	N/N	N/N	Y/N
Sex	N/N	Y/Y	Y/N	Y/Y
KPS		Y/N		
LDH		Y/Y		Y/Y
Low albumin		Y/Y (≥4 g/dL)		Y/Y (≥3.5 g/dl)
Plt>400,000		Y/Y		
Prior Rx None Surgery Immuno Chemo		N/N		
No. of initial metastatic site 1 vs 2 or more	Y/Y	Y/N	Y/N	
Initial site of metastasis Soft tissue Lung Liver, bone, brain	Y/Y		Y/Y	
Initial site of metastasis Non-visceral** Visceral ***	Y/Y	Y/Y		

* Univariate/Multivariate: Y means “statistically significant”and N means “not statistically significant”

**non-visceral sites: skin, subcutaneous, lymph nodes

***visceral sites: any sites other than skin, subcutaneous, or nodal metastases

Liver involvement with metastatic melanoma has not been demonstrated to be an independent prognostic factor for poor survival. Sirrot et al found that liver involvement was not of prognostic value by multivariate analysis in 284 patients. In a phase III trial of DTIC versus DTIC plus interferon versus DTIC plus tamoxifen versus DTIC plus interferon plus tamoxifen (N=271), Falkson et al found no significant difference in overall survival among any of the treatment arms. In the Cox proportional hazard model for the endpoint of overall survival, the presence of liver metastases was not a significant prognostic factor (11). Median survival data is lacking in patients presented with liver involvement from primary skin melanoma at the initial diagnosis of metastatic disease. Data from MD Anderson in 201 patients with ocular melanoma, which characteristically metastasizes to liver by hematologenous spread, showed that the median survival of those with liver metastasis was 7 months (12). In summary, **the considerable variability in survival in patients with liver involvement with metastatic melanoma indicated that other prognostic factors are important determinants of survival in these patients.**

For patients presenting with stage IV metastatic melanoma, treatment recommendations are governed by a number of observations. If evaluations reveal a solitary focus of metastatic disease, options for treatment include surgical resection if possible. If the solitary site is unresectable and/or the work-up uncovers other sites of disease, treatment options include a clinical trial or systemic therapy with dacarbazine (DTIC), either as a single agent or in combination with other agents. In selected patients with a solitary site of visceral metastatic melanoma, a short period of observation may be appropriate to rule out the possibility that the visceral metastasis is just one of many metastatic sites, and to select patients who would be most appropriately treated by surgical intervention. For patients with unresectable distant metastatic disease unresponsive to investigational treatment or single-agent dacarbazine, subsequent therapeutic options include dacarbazine-based combination chemotherapy, participation in another clinical trial, or best supportive care.

Single agent DTIC is associated with a response rate of about 20%. Patients with skin, subcutaneous tissue and lymph node involvements are those most likely to respond. The median duration of response is 5-6 months. Complete responses are observed in about 5%, mostly in subcutaneous and lymph node metastases. A minority (31%) of patients who achieve complete response survive and remain disease-free at 6 years. Overall, about 2% of patients treated with DTIC are long-term complete responders (13). Combination chemotherapy containing DTIC and other agents may produce higher response rates but are generally more toxic than single agent DTIC.

The survival benefit of combination chemotherapy over single agent DTIC has not been demonstrated in randomized trials.

Immunotherapy using IL-2 alone or IL-2 and interferon alpha generates a response rate of 10-20%. The initial clinical studies done by Rosenberg et al at the National Cancer Institute using IL-2 with or without lymphokine-activated killer (LAK) cells, suggested that IL-2 had antitumor activity against metastatic melanoma. There have been numerous clinical studies testing IL-2 as a single agent in advanced melanoma. Eight of these published clinical studies were pooled and submitted to FDA in December 1997 to support marketing approval of IL-2 for the treatment of advanced melanoma. These eight phase II trials enrolled a total of 270 patients and reported a 6% complete response rate (CR) and 10% partial response rate (PR). The overall median duration of response was 8.9 months. The median duration of CRs had not been reached and was >40 months. The median duration of PRs was 5.9 months. Overall median survival of 270 patients was 11.4 months and the survival rate at 24 months was approximately 22%. Survival data on subgroups of patients, e.g., those with liver metastases at study entry, were not available, but 70% of the study population had visceral disease and more than one site of metastases at study entry. Data were not available on patients with liver metastasis. Patients with ECOG performance status 0 had twice the response rate of those with performance status 1 and the PR was doubled for patients with no prior systemic therapy. Individual data on patients who experienced CR revealed that 2/17 had liver metastases. Those 2 patients also had lung and CNS metastases. Similar data in patients who experienced PRs revealed that 7/26 had liver metastases. Although response rate was numerically higher in patients with visceral disease (20% vs. 14%), it was not statistically significant. High dose bolus IL-2 (720,000 u/kg IV every 8 hours for 5 days) repeated 6-10 days later was approved by FDA for the treatment of metastatic melanoma based on durable long term partial and complete responses.

6. Major trial

This NDA contains one major randomized, controlled trial (MP-US-M01) and four supportive studies: M103, MM-1, MM-2, MM-3. Since the treatment regimen in MM-1, MM-2 and MM-3 is significantly different from the one used in MP-US-M01, these three studies will not be reviewed.

6.1. Protocol Review

6.1.1. Protocol overview

Study MP-US-M01 is a twelve-month, multi-center, open-labeled randomized controlled study in patients with metastatic melanoma.

Investigators: No designated principal investigator

Study Centers: 56 Institutions in United States

Study Period: The first patient enrolled on 7/3/97.

Data cut-off date: 3/8/2000 (12 months from the date on which the 300th patient was randomized into the study)

Review of Protocol Amendments (non-administrative or editorial changes)

Amendment 1 (7/23/97):

- Required Day 1 and 8 treatment be administered under the supervision of healthcare professionals in the clinic

Amendment 2 (7/29/97):

- Clarifications on inclusion and exclusion criteria
- Defined sentinel lesions as all measurable lesions at baseline that, in the clinical judgement of the investigator, most clearly represent the state of disease.
- Patients with progression of disease documented by imaging studies on week 12 were to continue treatment and have a repeat imaging study at week 18. The week 18 imaging study would be compared to imaging studies at baseline and at week 12.

Amendment 3 (8/18/97):

- Clarifications of inclusion and exclusion criteria
- Expanded the pre-study window from 2 weeks to 3 weeks

Amendment 4 (12/3/97):

- Added esophageal ulcer disease as an exclusion criterion
- Added weekly toxicity evaluations in weeks 5 and 6 of each cycle
- Changed the criterion for discontinuing therapy due to progression of disease (i.e., patients with >25% increase in all measurable disease at week 18 compared to imaging studies at week 12 should be considered to have progression of disease and should be removed from the study)
- Allowed 4 additional cycles of therapy i.e., 6-month treatment after patients completed 12-month therapy; no crossover was allowed.

Amendment 5 (2/26/98):

- Changes in preparation of IL-2 and formulation of histamine dihydrochloride
- Added that patients who had a significant drop in blood pressure while receiving treatment should have hydration status checked and vital signs monitored before and after receiving treatment.

Amendment 6 (11/28/98):

- Eligibility criterion was changed to permit patients who had received radiation therapy to the indicator lesion ≥30 days before randomization and patients with resolved or controlled brain metastases to enroll in the study.
- **Eligibility criterion was changed to require only histologically proven primary melanoma i.e., histologic proof of metastatic disease was not required**
- Added to eligibility criteria : PT within normal limits and normal cardiovascular stress test for patients ≥50 years of age and for younger patients with a history of cardiac disease
- Added to the exclusion criteria that patients with hyperglycemia, requiring glyburide, or a history of autoimmune disease be excluded from the study
- Added that measurement of tumor lesions could be done by palpation and other acceptable methods; added that skin lesions should be documented by photographs
- Clarified that measurable disease could be a single lesion >2cm x 2 cm or multiple lesions with one lesion >1 cm x 1 cm or unidimensional lesion >2 cm
- **Allowed radiation as palliative treatment for lesions that are not used to measure response while on study**
- Clarifications on the exclusion of patients receiving concomitant steroid, anti-hypertensive medications, H_2 agonist or beta-blocker therapy
- **Added that the presence or absence of liver metastasis was to be recorded.**
- **Added that the Quality of Well-Being was to be completed by the patient at the end of each treatment cycle, and prior to receiving the first dose of study medication for the next cycle.**
- **Increased sample size from 240 patients to 300 patients**
- Added that medical resource utilization and costs were to be assessed
- **Added that a dose reduction was allowed for <grade 3 toxicities if the toxicity affected the patient's quality of life**
- Allowed antihistamines (H_1 antagonist) to be used for less than 5 days to treat acute colds or seasonal allergy symptoms but required the antihistamines be stopped >24 hours prior to Day 1 of Cycle 1.
- Clarified that prohibited medications must be stopped > 24 hours prior to Day 1 of Cycle 1.

- Clarifications on tumor response evaluation
- **Added that patients would be allowed up to a 2-week drug holidays after completing a minimum of 4 cycles; additional drug holidays were allowed between weeks 2 and 3 of cycles 5-8 as deemed necessary by the investigator. No more than 2 drug holidays were allowed during cycles 5-8. Cycles would be 8 weeks long with 4 weeks of treatment. Holidays must be taken in 1 week increments.**
- **Added that patients will be followed every three months after the treatment period until either three years after onset of treatment or until patient death, to determine performance status and disease state.**
- Added that patients with partial remission, minimal regression or stable disease were to be re-evaluated for confirmation of response at week 18. If the response was confirmed at 18 weeks, the patient was to be monitored every 12 weeks. If the response had changed at 18 weeks, the patient should be re-evaluated at 24 weeks.
- Added that patients with complete response after the week 12 evaluation, may continue for the entire treatment period of 12 months, enter the 6-month extension period, or may be removed from the study treatment.
- **Added that patients with progressive disease after the week 12 evaluation were to be re-evaluated at week 18. If a patient's performance status had not changed, the patient should continue on study and be re-evaluated every 6 weeks. Biopsies were recommended to verify progression of disease versus an active immune response at the tumor site**.
- Added that all safety and efficacy evaluations were to be carried out when a patient was removed from the treatment from any reason.
- Clarified the adverse event definitions and reporting process.

<u>Amendment 7 (9/21/99):</u>

- **Deleted the requirement of a repeat MRI scan of brain at week 12**
- **Added that patients were to be followed every 3 months after the treatment period for disease recurrence and survival as long as they lived**
- Added that if the circumstances of the patient 's relapse met the SAE definition, it would be captured as an SAE. Any death that occurred while the subject was participating in the study was to be captured as an SAE. Death due to progressive disease would not be considered to be caused by the use of Histamine/IL-2. Death due to progressive disease would be submitted to a regulatory agency as an expedited report if it were considered to be related to the use of Histamine/IL-2.

- **Added that the ITT population would include all patients who had been randomized into the study and was to be the primary analysis population.**

Revisions of statistical analysis plan:

6/25/99: The applicant provided a detailed statistical analysis plan. Primary efficacy endpoint was overall survival and secondary endpoints were time to treatment failure, response rate, duration of response, and relapse-free survival with 12-month follow-up. Prognostic factors such as center region (East, West, North, South), age, sex, race, patient's metastatic disease sites at first evaluation (skin/lymph, lung/GI/kidney, liver/bone), number of disease sites, prior anti-cancer therapies, WHO performance status, duration of therapy prior to randomization, LDH, prior chemotherapy, and current treatment assignment would be assessed in conjunction with the primary efficacy endpoint. These covariates would be explored separately using univariate models with treatment and covariate of interest at the 0.05 alpha level. Covariates would also be explored multivariately using the automated backward selection method with the Cox model at the 0.05 alpha level with treatment and center, where applicable, retained in the same model. Three subsets would be analyzed. The intent-to-treatment subset defined as all patients who have been randomized into the study would be used as the **primary subset**. The evaluable subset for safety would include all patients who have received one dose of study medication, and the evaluable subset for efficacy would include all patients who satisfied all protocol-required entry criteria, received a minimum of six weeks of therapy with verification of compliance with scheduled study assessments, and received no concurrent anti-cancer treatment. All efficacy endpoints would be summarized for a subgroup of patients who entered the study with liver metastases. **The primary assessment would be overall survival in the ITT subset and liver metastases subgroup.** Sample size was increased to 300 patients.

9/15/99: Two subsets would be analyzed, the ITT subset of all patients who have been randomized into the study and a evaluable for safety subset who had received one dose of study medication. The primary efficacy endpoint would also be assessed in the following subgroups: ITT patients who entered the study with liver metastases, ITT patients recruited in experienced centers (with at least seven randomized patients), and patients with liver metastases in the experienced centers. The analysis of primary efficacy endpoint (overall survival) would be performed on the ITT dataset and for all subgroups derived from the ITT dataset.

11/18/99: The applicant added the statement that two hypotheses would be tested in this study.

Null hypothesis No.1: Histamine 1 mg/ml given by subcutaneous injection in conjunction with IL-2 did not improve the duration of survival of patients with advanced malignant melanoma compared to treatment with IL-2 alone.
Null hypothesis No.2: Histamine 1 mg/ml given by subcutaneous injection in conjunction with IL-2 did not improve the duration of survival of patients with advanced malignant melanoma who had liver metastases at study entry compared to treatment with IL-2 alone. The ITT population of all randomized patients would be the dataset for testing the first hypothesis. ITT-liver Mets Population (ITT-LM) was a subset of the first and consisted of all randomized patients with liver metastases at study entry. **The primary endpoint of survival would be compared between the two treatment groups for the two populations i.e., ITT and ITT-LM. The primary endpoint of survival would be adjusted for multiple comparisons at the 0.05 family-wise Type I error using the Holm-Sidak step-down procedure ("sharper Bonferroni Procedure"). Additional supportive analyses would include a stratified Cox model by liver metastases at baseline (or not) using treatment as the covariate, and Cox adjusted covariate analyses including covariates other than treatment in the model.** In the Cox model, handling of possible tied event times would be made using the "exact" method. The secondary endpoint of time to treatment failure was changed to time to progression.

6.1.2. Study objective

The primary objectives of this study were to evaluate the safety and efficacy of histamine dihydrochloride when given in combination with IL-2 as compared to IL-2 alone, in patients with stage IV metastatic melanoma who had not been treated or had failed other first line therapies.

6.1.3. Patient population

Inclusion Criteria:

- Histologically proven melanoma that has progressed to Stage IV
- Patients may be untreated, or may have received previous regimens of chemotherapy, radiation therapy, immunotherapy other than IL-2

- ≥1 bidimensionally measurable masses (in some cases, unidimensional lesions will be acceptable); measurements could be made by x-ray, CT or MRI scans, palpation or other acceptable methods; If one lesion, it had to be ≥2 cm x 2 cm bidimensionally; if multiple lesions, at least one lesion had to have the minimum size of 1x 1 cm; unidimensional lesions were acceptable if greater than 2 cm.
- Nuclear bone scans, pulmonary lymphangietic metastases, and blastic bone lesions on skeletal x-rays were not considered measurable or evaluable. Pleural effusions or ascites were evaluable but not measurable. Unmeasurable palpable masses, diffuse hepatomegaly, or serological tumor markers were not evaluable.
- Patients with prior radiation therapy were allowed, provided that the indication lesion(s) was (were) outside the field of radiation or represent new lesions appearing in the radiation field.
- Patients with prior radiation therapy to the indicator lesion were eligible if the radiation therapy occurred greater than 30 days prior to randomization.
- Age ≥18; able to give informed consent, female patients who were not pregnant (negative pregnancy test within 2 weeks, non-breast feeding, and on effective contraception)
- No serious medical or psychiatric condition
- Life expectancy>3 months
- WHO KPS 0-1 corresponding to Karnofsky status ≥70%
- Must be at least 14 days from previous therapy (including corticosteroids) and have recovered from the toxicity from previous therapy
- Adequate bone marrow reserve, liver , renal function
  - WBC>2500, ANC>1500, Plt>100,000, Hb>10
  - Normal PTT
  - Serum creatinine <1.5, serum glucose <160
  - Normal AST or total bilirubin unless liver involved with tumor then AST<3 x ULN, bilirubin<1.5 x ULN
- Normal cardiac function; for all patients ≥50 yrs old, and patients ≤49 yrs old with a positive cardiac history or an abnormal cardiogram, a cardiovascular stress test was required to document normal ejection fraction and wall motion.

Exclusion Criteria:

- Any concurrent systemic antimaligancy therapy or radiation therapy to measurable malignant masses, except for radiation as palliation treatment for lesions that were not used to measure response
- Patients requiring steroidal therapy for any reason 24 hours prior to the first dose of study drug and throughout the duration of the study

- Primary or metastatic CNS tumor; patients with CNS metastasis that had been completely resected or resolved and controlled were allowed.
- Active infection requiring ongoing specific therapy.
- Organ graft other than autologous bone marrow or stem cell transplant
- Previous documented history of asthma actively treated in the last five years
- Patients with active peptic and/or esophageal ulcer disease or with a history of bleeding peptic ulcer disease
- Systemic allergic reaction or drug-dependent asthma
- History of seizure, CNS disorder, psychiatric disorder or sociologic impediment to adversely affect compliance to protocol
- Hypercalcemia >11.5
- Respiratory insufficiency defined by SaO_2<90% and FEV1/FVC<70% of predicted
- HIV positive or prior history of autoimmune disease
- Alternative therapies such as laetrile, Brudzinski's treatment, etc.

Reviewer's comment:
The protocol initially required histologically proven progressive stage IV melanoma and was amended to require only the primary tumor (NOT the metastatic disease) be histologically proven melanoma.

6.1.4. Randomization (Volume 2.22 study report)

Patients were randomized to one of the two treatment groups by the central desk according to the treatment assignment code. Randomization was done in consecutive sequence within each center. The randomization table was prepared by a statistician in blocks of four at each center so that within each block of four, two patients would be randomized into each treatment arm. The randomization was controlled from a single location, administered by [ ], the contract research organization assigned responsibility for this portion of the study. After determining each patient's eligibility for enrollment, principal investigators telephoned [ ] to determine treatment arm assignment. Therapy was to start within two weeks following randomization.

Reviewer's comment: No stratification for important prognostic factors in metastatic melanoma was performed.

6.1.5. Treatment Plan

The first two high dose treatments were to be given in the clinic or the physician's office. The rest were administered in the outpatient setting.

Patients were given one week supply of IL-2 /Histamine or IL-2 (pre-loaded syringes or multidose vials).

Table 3. Treatment Regimen Used in MP-US-M01

Treatment	Six-Week Cycle Regimen
Interleukin-2	9.0 MIU/m^2, SC , BID, days 1 and 2 of weeks 1 and 3 2.0 MIU/m^2, SC , BID, days 1 through 5 of weeks 2 and 4 Rest, weeks 5 and 6
Interleukin-2	9.0 MIU/m^2, SC , BID, days 1 and 2 of weeks 1 and 3 2.0 MIU/m^2, SC, BID, days 1 through 5 of weeks 2 and 4
Histamine	1 mg, SC , BID, days 1 through 5 of weeks 1 through 4 Rest, weeks 5 and 6

Histamine was administered by slow SC injection of not less than 10 minutes. IL-2 was always administered 5-10 minutes before histamine.

Patients were allowed up to a 2 drug holidays during the treatment period after completing a minimum of 4 cycles. Holidays were to be taken in 1-week increments. Additional drug holidays were allowed between weeks 2 and 3 of cycles 5-8 as deemed necessary by the investigator, and approved by the Medical Monitor. No more than 2 drug holidays would be allowed during cycles 5-8.

Treatment was to continue until **clinically significant** disease progression unless life-threatening toxicity or complications occurred. Patients were to remain on the treatment regimen if disease progression was clinically insignificant changes in sentinel lesions that did not cause a change in WHO performance status by 1 or a decrease in Karnofsky performance status of 20 points during treatment.

Patients were considered to have completed the study treatment after finishing 8 cycles. The treatment period would include the time from the first dose to 28 days following the last dose of study drug for safety assessment. The onset of all new adverse events and the initiation of all concomitant medications were to be documented in the patient's Case Report Form. Patients were to be followed every three months for disease recurrence and survival as long as they lived.

Reviewer's comment:
It is unclear from the protocol how often patients were to have imaging studies assessing disease state after they completed the treatment.

6.1.6. Dose Modification

Grade 3 toxicities (except those listed above)---hold IL-2 until toxicity returns to Grade 2 or less. Permanent 50% reduction in IL-2 dose. Restart histamine at an increased injection time of 20-30 minutes. If toxicity continues, reduce histamine dose by 50% at the extended injection time.

Grade 4 toxicity or recurrent grade 3 toxicity despite dose reduction---off study

Dose reduction for specific toxicities:

- SBP<80mmHG---hold IL-2 and histamine until SBP normalizes then restart IL-2 at 50% of the scheduled dose and increase the administration time of histamine to 20 minutes; for histamine-induced hypotension with SBP< 80mmHg, increase the injection time from 10 minutes to 20 minutes. If hypotension persists, then lower the histamine dose by 50% to 0.5mg/0.5 ml to be infused over 20 minutes; symptomatic hypotension despite a 50% reduction in IL-2 dose, take off study
- Histamine-induced headache, flushing: no dose reduction for flushing; increase the injection time to 20 minutes for grade 3 headache
- Hematologic toxicities: if treatment delay< 2 weeks and toxicity is grade 2 or 3, 50% reduction in IL-2 dose; if treatment delay> 2 weeks, take off study
- Cardiac toxicity: hold all therapy for sinus tachycardia (pulse> 140/min) or atrial dysrrhythmias; when atrial dysrrhythmias resolve, 50% dose reduction in IL-2 and increase histamine infusion rate to 20-30 minutes; If atrial dysrrythmia recurs, take off study; if myocarditis during treatment (elevated CPK MB and/or decreased ventricular function), take off study
- Neurologic toxicity: hold for grade 2 neurologic toxicity; after resolution, 25% reduction in IL-2 dose

Other Grade 1-2 toxicities: **dose reduction allowed if the toxicity affected the patient's quality of life**

Criteria for treatment: ANC>1000, Platelet >100,000 and <grade 2 non-hematological toxicity

Removal from treatment: grade 4 toxicity or Grade 3 toxicity on reduced dose; symptomatic hypotension despite a 50% reduction in IL-2 dose; a treatment delay >2 weeks; progression of disease for at least two consecutive treatment cycles or clinical deterioration at any time during the study; recurrent atrial dysrrythmia despite a 50% dose reduction of IL-2; patient withdrawal; investigator's discretion.

6.1.7. Evaluations during study

Please see the following “activity chart”.

Table 4: The applicant's activity chart

5.2 Activity Chart	Prestudy (prior to Randomization	Cycle 1 Day 1	Cycle 1 Week 2 Day 1	Weekly (prior to study drug)	q 6 Weeks	q 12 Weeks
Informed consent	X					
History and PE, Vital Signs	X				X	
Performance Status	X	X		X		
Quality of Well-Being	X				X	
Tumor Measurements	X					1
Chest x-ray (CT scan may be used)	X					1
CT scan of the chest	2					1
MRI brain scan	X					
CT or MRI scans of abdomen	X					1
CT or MRI scans of the pelvis	3					1
EKG	X					X
Cardiovascular Stress Test	4					
Hematology:						
CBC*, Platelet	X			X		X
Chemistry:						
Bilirubin, SGOT (AST), alkaline phosphatase, albumin, total protein, calcium, glucose, phosphorus, CPK, LDH	X					X
Serum creatinine, BUN, Na, K, Cl, CO2	X			X		X
TSH/T4, PTT, PT	X					
Urinalysis	X					X
Serum HIV	X					
Pregnancy Test	X					
Toxicity & AE Evaluation	X	X		X		
Pulse Ox/Respiratory Function	X					
Vital Signs Measurement Pre IL-2 injection Post IL-2 injection Post Maxamine injection	X	X (AM/PM)	X (AM)		X	
30 Second Rhythm Strip 30 minutes post IL-2 or Post IL-2/Maxamine injections		X (AM)	X (AM)		X	

[1]All patients were required to have 12 and 18 week scans; Quality of Well-being was to be completed by the patient at the end of each treatment cycle and prior to receiving the first dose of study medication for the next cycle.
[2]CT scan of the chest to be performed if the chest x-ray was abnormal or mediastinal disease was suspected
[3]CT scan of the pelvis was to be performed if pelvic metastases were suspected
[4]Performed on all patients ≥50 yrs old and on patients <50 yrs if EKG was abnormal or the patient had a positive cardiac history.

Assessments of medical resource utilization and costs were to be performed using data on economically significant health care services provided outside the clinical protocol. These medical encounters included all hospitalizations and any medical services related to an adverse event, serious adverse event or other economically significant medical encounter. Medical resource data on inpatient stays, surgical interventions and economically significant outpatient encounters were to be collected on the Medical Care Resource Utilization Form. This form would be filled out by the site monitor at each scheduled monitoring visit for every patient when a medical encounter occurred that met the criteria listed above. Data from the Medical Care Resource Utilization Form would be supplemented with data from the clinical database, including the Concomitant Medications form or Serious Adverse Event narratives. Cost would be assigned to the resource utilization data using external sources on medical costs and incorporated into the comparison of the two treatment groups.

Patients who completed 12 months of therapy could continue on their previously assigned arms for an additional 6 months. Patients would be evaluated every 6 weeks during this extension period. All patients were to be followed for survival.

Reviewer's comment: The protocol did not specify whether imaging studies of tumor would be performed regularly during the extension and follow-up period.

6.1.8. Concomitant medications

Beta blockers, antihypertensives, steroidal medications and H_2 antagonists were to be stopped 24 hours prior to Day 1 of Cycle 1, and were not allowed throughout the study. Antihistamines (H_1 antagonists) were allowed for <5 days for acute colds or seasonal allergy symptoms but could not be given within 24 hours of Day 1 of Cycle 1.

6.1.9. Efficacy assessment

Response would be assessed as follows: **a minimum of one and then all measurable, as per the minimum dimension criteria, sentinel or non-sentinel lesions were to be selected for determining the efficacy of study treatment**. Sentinel lesions were defined as all measurable lesions existing at baseline that most clearly represent the state of disease in the clinical judgement of the investigator. Sentinel lesions were selected before treatment began and could not be in previously irradiated fields unless

progression had occurred or these were new lesions. Sentinel lesions had to have a minimum size, as specified in the protocol. The liver span itself could not be used as a sentinel lesion, although lesions within the liver could be used as sentinel lesions. Responding patients would need imaging studies repeated 28 days later to confirm the response.

Disease was measurable if the patient had one or more lesions that were clearly demarcated and could be measured in millimeters. Bidimensional disease should be measured by two perpendicular measurements of the lesion. The first measurement was the longest span of the lesion and the other measurement was the longest span perpendicular to the first measurement. The size of the lesions was the product of these two measurements. Unidimensional sites of disease were acceptable if ≥2cm. The overall size of sentinel lesions was the sum of the bidimensional disease products of the two dimensions recorded for each lesion.

- CR: total disappearance of tumor and tumor related symptoms; response must be confirmed by a second measurement 4-6 weeks following the original observation.
- PR: ≥50% decrease in the overall tumor size of the **sentinel lesions** as compared to measurements taken at baseline and maintained for 4-6 weeks; no simultaneous increase in the size of any other lesion (non-sentinel or non-measurable) or appearance of new lesions. Surgical removal of responding sentinel lesions was permitted but this was still considered a partial response. After the week 12 evaluation, patents were to be re-evaluated for confirmation of response at week 18. If the response was confirmed at week 18, patients were to be monitored every 12 weeks. If the response had changed at week 18, patients were to be re-evaluated at week 24.
- MR: same as PR except 25-50% decrease from the baseline size of the sentinel lesions.
- Stable disease: no more than a 25% increase or decrease in the overall size of all sentinel lesions and no new lesions had appeared.
- Progression: **>25% increase in the sum of the sizes of all sentinel lesions, a 50% or greater increase in the size of any single lesion, the appearance of a new lesion during two consecutive cycles of treatment or death caused by malignancy**. Tumor size from the week 12 evaluation was to be compared to baseline; tumor size from evaluations performed after week 12 was to be compared to week 12 and baseline unless a decrease in tumor occurred, in which case progression would be measured from the tumor size nadir. Patients were to be re-evaluated for confirmation of progressive disease at week 18. If the patient's performance

status had not changed, the patient were to continue on study and be re-evaluated every 6 weeks. Biopsies were recommended to verify progression versus an active immune response at the tumor site.

- Response duration: measured from the date when the objective response criteria were first met until disease progression.
- Survival: measured from the date of randomization into the study until death or the date last known alive, counting all deaths as events.

Reviewer's comment:
The definition of progression of disease was confusing. The 25% or more increase in tumor size applied only to sentinel lesions and did not take into account the size increase in the non-sentinel lesions. According to the protocol, only one sentinel lesion was required to be selected for following response or progression.

6.1.10.Safety assessment

Monitoring for toxicities was performed weekly during the study, and graded using the CALGB Expanded Common Toxicity Criteria /NCI Common Toxicity Criteria. The protocol listed the following expected adverse events of histamine: transient hypotension, tachycardia and tachypnea, mucosal congestion, coughing, urticaria, rash, facial flushing, metallic taste, transient headache, and possible aggravation of asthma.

The protocol stated that IL-2 administration had been associated with capillary leak syndrome (CLS), which results from extravasation of plasma proteins and fluid into the extravascular space and loss of vascular tone. CLS can result in hypotension and reduced organ perfusion, which may be severe and can result in death. The CLS may be associated with cardiac arrhythmias, angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, and mental status changes. Intensive IL-2 treatment is associated with impaired neutrophil function and an increased risk of disseminated infection in treated patients.

6.1.11. Statistical plans

The original plan was to enroll 200 patients with metastatic melanoma in 8-10 centers. The primary endpoint was survival and the survival curves for the two treatment groups would be compared using a log-rank test. The survival curves would be adjusted for prognostic variables such as cutaneous, GI, nodal

lesions and pulmonary lesions based on the location of the patient's metastatic disease at first evaluation. Patients would be "stratified" in subgroup analyses accordingly: a) liver metastases or not; and b) previously treated with DTIC or previously untreated, using Cox regression models.

Subsequently, the sample size was increased to 240 patients. According to the applicant, enrollment of 120 patients in each group would be required to maintain a 80% power to detect a 50% increase in median survival time (7.3 months to 11 months) between the two treatment groups with a type I error of 0.05 (assuming a dropout rate of 20%).

The sample size was further **increased from 240 patients to 300 patients** in protocol amendment 6 dated 11/28/98. The applicant stated that an increase in sample was necessary to maintain the 80% power to detect a 50% increase in median survival with an accrual time of 18 months, assuming a 15% dropout rate.

In the most recent protocol dated 9/21/99, **the primary efficacy analysis was to be performed on an "intent-to-treat" basis using all patients who were randomized into the study.** Results would also be displayed for patients presenting with liver metastases versus patients with patients with no liver metastases, and patients previously treated with DTIC versus DTIC naïve patients. Secondary efficacy parameters were time to tumor progression and tumor-free survival.

In the final statistical analysis plan dated November 18, 1999, the **primary efficacy endpoint was overall survival.** An unadjusted log-rank test would be used as the primary analysis comparing the Kaplan-Meier survival distribution curves between the two treatment groups **within two populations:** All randomized patients on an Intent-to-Treat basis (ITT population) and all randomized patients with liver metastases at baseline (ITT-Liver Mets population). The primary endpoint of survival was to be adjusted for multiple comparisons at the 0.05 family-wise Type I error rate using the Holm-Sidak Step-Down Procedure (sharper Bonferroni Procedure). Cox proportional hazards model (adjusting for significant covariates) would provide supportive information in the determination of efficacy with respect to overall survival. The following covariates would be used in the Cox models: treatment (IL-2 vs. histamine/IL-2), age, sex, race, number of prior anti-cancer therapies (none vs. more than one), disease sites (skin/lymph/non-visceral, lung/GI/kidney/adrenal, liver/bone), number of disease sites, LDH, prior chemotherapy, baseline performance status, center (geographic region-North, South, Mid-West, West). These covariates would be explored separately using univariate models with treatment and covariate of interest at the 0.05 alpha

level. Covariate would be explored in a multivariate manner using the automated backward selection method within the Cox model at the 0.05 alpha level with treatment and center, where applicable, retained in the same model.

Secondary parameters were time to tumor progression, tumor response rate and duration of response. "Quality of patient's well being " would be analyzed using appropriate statistical methods. Quality of life analysis was submitted in a protocol amendment dated March 3, 2000. This protocol amendment was not submitted in this NDA.

The safety analysis would include all subjects who have received at least one dose of study medication. Each adverse event would be counted only once for a given patient. If the same adverse event occurs on multiple occasions, the highest severity and least complimentary relationship would be assumed.

Reviewer's comments:
The subpopulation of patients with liver metastases was designated one of the primary analysis population less than four months before the cut-off date of 3/8/2000. Quality of life analysis plan was submitted on 3/3/2000.

6.2. Trial results

The clinical study report of MP-US-M01 was in volume 2.22 of the NDA.

6.2.1. Study execution

A total of 305 patients enrolled in the study. Of these, 129 patients had liver metastases at study entry (liver metastases subpopulation i.e., ITT-LM). A total of 303 patients were included in the safety population. Of 153 patients randomized to the IL-2 group, 152 received at least one dose and were evaluable for safety. 152 patients were randomized to the histame/IL-2 group and 151 were evaluable for safety. Of the 56 centers that enrolled patients, 30 treated their patients an average of ≥2 cycles; these centers contributed 219 patients (72%). 13 centers enrolled 7 or more patients for a total of 188 patients (62% of the total enrolled), 95 patients in the IL-2 arm and 93 patients in the histamine/IL-2 group. Ten of the 13 centers enrolling ≥7 patients also treated their patients an average of ≥ 2 cycles of therapy.

<u>Ineligible patients:</u>
According to the applicant, 139 patients had enrollment violations.

Of the 66 ineligible patients in the IL-2 group (43%), enrollment exceptions were granted for 50 patients. An exception to enter the study was not requested by the investigator in the remaining 16 patients. The most common exceptions granted in the IL-2 group concerned abnormal hematology lab results (inclusion criteria #9; N=16), measurable disease criteria, and date of radiology scans to measure baseline disease (inclusion criteria #3; N=13). Additional exceptions were granted for issues other than the inclusion and exclusion criteria (N=10). Five exceptions were granted allowing substitution of CT head scan for MRI brain scans (N=5).

Of the ineligible 73 patients in the histamine/IL-2 group (48%), enrollment exceptions were granted for 56 patients. For the remaining 16 patients, no exception was requested by the investigator. The most common exceptions granted in the histamine/IL-2 group concern measurable disease criteria, radiological scans to measure baseline disease performed greater than 3 weeks prior to study entry (inclusion criteria #3; N=14), abnormal hematology laboratory results (inclusion criteria #9; N=6), abnormal cardiac function, the presence of cardiac disease or a positive stress test (inclusion criteria #8 N=4, exclusion criteria #3, N=4). Exceptions were granted for substitution of CT scans of the head for MRI brain scans (N=3). Additional enrollment deviations were noted, but the applicant stated that these deviations were not considered significant enough to affect the efficacy or safety results of the study.

FDA analysis used the electronic dataset provided by the applicant. In the dataset named "include", only 71 patients (34 on IL-2, 37 on histamine/IL-2) had responses on all 16 eligibility items. 87 patients violated at least one of the inclusion criteria (42 on IL-2, 45 on histamine/IL-2) and details on violation were not provided by the applicant.

Table 5: FDA Analysis of Ineligible Patients Based on Inclusion Criteria

No. of ineligible patients		Reason for Ineligibility
IL-2	H/IL-2	
0	2	? received prior IL-2
17	14	Did not meet the measurable disease criterion (#3)
0	1	Did not meet the adequate marrow, kidney, cardiac, or liver function criteria (#5)
18	13	Did not meet hematologic or coag criteria (#6)
2	2	Did not meet serum creatinine criterion (#7)
3	4	Did not have normal cardiac function (#8)
3	4	Did not meet the LFT criteria (#9)
2	4	Did not meet the fasting glucose criterion (#10)

2	3	Had not recovered covered from toxicity or had antimalignancy therapy within 14 days of entry(#11)

In the dataset named "exclude", 121 patients on IL-2 and 115 patients on histamine/IL-2 had no answer marked for exclusion criterion #19 (the use of glyburide). 133 patients on IL-2 and 115 on histamine/IL-2 had no response to the question on exclusion criterion #20 (i.e., taking prohibited medications). 30 patients violated at least one exclusion criterion (13 on IL-2, 20 on histamine/IL-2) and findings were summarized in Table 6.

Table 6: FDA Analysis: Ineligible Patients Based Exclusion Criteria

No. of ineligible patients IL-2	H/IL-2	Reason for being ineligible
0	3	Received prior IL-2 (#1)
0	3	Had clinically active infection (#2)
4	0	Had cardiac disease or positive stress test (#3)
1	2	Had other active malignancies (#5)
2	2	Had CNS metastasis (#6)
0	2	Had recent medical complications (#7)
1		Had active asthma within in the past 5 yrs (#9)
3	3	Had respiratory insufficiency (#15)
0	1	Had positive HIV or autoimmune disease (#16)
0	1	Had active peptic and/or esophageal ulcer disease (#18)
1	0	On glyburide (#19)
2	0	Took prohibited medications (#20)

Protocol violations: The applicant only provided information on violations of eligibility criteria in the clinical study report. No information on protocol violations that occurred on study was provided. **The applicant stated that this information was not systematically collected.** When the FDA reviewer examined the electronic dataset, a number of protocol violations were identified.

According to FDA analysis, 47 patients did not have the Cycle 1 Day 1 assessment of performance status (PS) required by the protocol and in those who did have a PS recorded, **18 had PS ³2 on Cycle 1 Day1 despite a baseline PS recorded as 0-1. All these 18 patients were treated with**

the assigned study medication, except one patient randomized to histamine/IL-2 arm who was not administered histamine.

Table 7: FDA assessment of patient performance status on Cycle 1 Day 1

	ITT IL-2 N=153	ITT H/IL-2 N=152	ITT-LM IL-2 N=77	ITT-LM* H/IL-2 N=54
Missing (N=47)	23	24	10	10
KPS=2 (N=12)	8	4	4	2
KPS =3 (N=3)	2	1	2	1
KPS= 4 (N=3)	1	2	1	2

*patients with liver metastases at study entry

Although the protocol required the first dose on day 1 and day 8 of the cycle be administered under the supervision of a qualified healthcare professional within the clinic, 48 patients had no documented clinic visit date (24 on IL-2, 24 on histamine/IL-2) of Cycle 1 Day 1.

Approximately 38% of patients did not have the protocol required week 12 imaging studies. The number of missing imaging studies sharply increased at week 18. More patients on the IL-2 arm had missing imaging studies.

Table 8: FDA Analysis of Missing Imaging Studies

	ITT IL-2 N=153	ITT H/IL-2 N=152	ITT-LM IL-2 N=77	ITT-LM* H/IL-2 N=54
Missing Baseline				
Both CXR and chest CT	1	1	1	1
MRI brain	11	9	5	1
Abd CT	6	2	1	0
Missing at Week 12				
Both CXR and chest CT	63	53	34	21
Abd CT	65	60	31	19
Missing at Week 18				
Both CXR and chest CT	118	102	62	39
Abd CT	120	98	59	36
Missing at Week 24				
Both CXR and chest CT	128	116	60	44
Abd CT	129	118	61	41

*Patients with liver metastases at study entry

Compliance with medication was assessed by weekly patient diary. Return of multi-dose vials or prefilled syringes to check medication compliance was not required by the protocol. The assessment of medication compliance by the applicant is based on patient diaries and may not be accurate.

Table 9: FDA Analysis of the Maximum Number of Cycles Completed by Patients Using the Applicant's dataset Csum_dvd

Number of Patients	ITT IL-2 N=153	ITT H/IL-2 N=152	ITT-LM* IL-2 N=74	ITT-LM* H/IL-2 N=55
Did not complete 1 cycle (N=2)	1	1	1	1
Received total 1 cycle (N=65)	33	32	19	16
Received total 2 cycles (N=88)	52	36	26	8
Received total 3 cycles (N=60)	29	31	14	12
Received total 4 cycles (N=33)	14	19	4	7
Received total 5 cycles (N=22)	11	11	5	4
Received total 6 cycles (N=9)	2	7	1	2
Received total 7 cycles (N=4)	1	3	1	1
Received all 8 cycles (N=22)	10	12	3	4

*Patients who had liver metastases at study entry

Reviewer's comments:
Dose reduction of histamine was not captured on the CRF for histamine administration. The dose reduction section on the CRF for recording adverse events did not make a distinction between dose reduction of IL-2, or histamine or both. It appeared that only 30% of the study population received more than three cycles of treatment.

6.2.2. Baseline characteristics

The applicant reported that the two treatment groups in the ITT population were comparable in demographics except for the fact that there were more patients ≥65 yrs old in the IL-2 group (33% vs. 23%) and a higher percentage of males in the IL-2 group (65% vs. 59%). Other differences between the two groups were listed by the applicant in Table 10, below.

Table 10: Applicant's Analysis of Patient Demographics

	ITT IL-2 N=153	ITT H/IL-2 N=152	ITT-LM* IL-2 N=74	ITT-LM* H/IL-2 N=55
Age				
≥65 (%)	50 (33)	35 (23)	28 (38%)	13 (24)
Sex				
Male (%)	99 (65)	90 (59)	46 (62)	27 (49)
Baseline KPS				
PS 0 (KPS 90-100)	103 (67)	103 (68)	44 (59)	35 (64)
PS 1 (KPS 70-80)				
Baseline LDH				
>ULN	57 (40)	52 (36)	38 (56)	32 (63)
Disease-free interval**				
Unk	5 (3)	7 (5)	1 (1)	4 (7)
Median (yrs)	2.37	3.11	2.72	3.52
Range (yrs)	0-38.1	0.1-30.3	0.1-38.1	0.1-20.0
0-2 yrs	64 (42)	49 (32)	27 (36)	11 (20)
3-4 yrs	37 24)	42 (28)	21 (**28**)	18 (**33**)
>4 yrs	47 (31)	54 (36)	25 (**34**)	22 (**40**)
Number of disease site				
1	31 (20)	37 (24)	7 (9)	13 (**24)**
≥2	122 (80)	115 (76)	67 (81)	42 (**77**)
Disease sites				
Skin	40 (26)	47(31)	18 (24)	12 (22)
Lymph node	83 (54	77 (51)	38 (**51**)	24 (44)
Lung	90 (59)	99 (65)	47 (**64**)	32 (58)
Liver	74 (48)	55 (36)	74 (100)	55 (100)
Bone	11 (7)	19 (13)	8 (11)	5 (9)
CNS	10 (7)	12 (8)	6 (**8**)	1 (**2**)
Prior chemotherapy				
Yes	38 (**25**)	40 (**26**)	21 (**28**)	10 (**18)**

*Patients with liver metastases at study entry
**Disease free interval from the initial diagnosis of primary tumor

FDA analysis of patient characteristics confirmed **that there were many imbalances between the two treatment arms, especially in the subpopulation of patients with liver metastases at study entry (i.e., ITT-LM). Many of these imbalances were in known prognostic factors (e.g., number of disease sites, disease free intervals, and performance status) which were all in favor of the histamine/IL-2 arm.**

Table 11: FDA Analysis of Patient Characteristics

	ITT IL-2 (N=153)	ITT H/IL-2 (N=152)	ITT-LM* IL-2 (N=74)	ITT-LM* H/IL-2 (N=55)
Age				
Median	56	53	**58**	**53**
range	(21-89)	(22-84)	(25-88)	(31-79)
Sex				
Male (%)	99 (65)	90 (59)	46 (**62**)	27 (**49**)
Female (%)	54 (35)	62 ((41)	28 (38)	28 (51)
Baseline PS				
PS=0 (%)	103 (67)	103 (68)	44 (59)	35 (64)
PS=1 (%)	50 (33)	48 (32)	30 (**41**)	19 (**35**)
Unknown	0	1	0	1
Baseline LDH				
>ULN	57 (37)	52 (34)	38 (**51**)	32 (**58**)
Unknown	10 (7)	8 (5)	6 (8)	4 (7)
Baseline albumin				
≤4 g/dl	80 (52)	71(47)	46 (**62**)	28 (**51**)
≤3.5 g/dl	26 (17)	20 (13)	18 (**24**)	9 (**16**)
Unknown	1	2	0	1
Disease-free interval**				
Unknown	6 (4)	9 (6)	2 (3)	5 (9)
>365 days (12 months)	100 (65)	104 (68)	52 (**70**)	42 (**76**)
>548 days (18 months)	81(53)	87 (57)	43 (**58**)	39 (**71**)
>1460 days (4 yrs)	32 (21)	45 (30)	18 (**24**)	20 (**36**)
Time since initial metastasis ***				
Unknown	2	3	2	1
Median (days)	116	112	75	84
Mean (days)	298	315	313	302
Range	2-4952	7-2599	2-4952	7-2009
>365 days (12 months)	32 (21)	33 (22)	10 (**14**)	12 (**22**)
>730 days (24 months)	16 (10)	20 (13)	8 (11)	7 (13)
Number of disease site				
1	31	37	7 (9)	13 (**24**)
≥2	122	115	67 (91)	42 (76)
CNS metastasis	10	12	6 **(8)**	1 **(2)**
Skin/lymph node/lung only	31**(20)**	38 **(25)**	N/A	N/A
Prior chemotherapy				
Yes	38	40	21 (28)	10 (18)
No	115	112	53 (72)	45 ((**82)**

* Patients with liver metastases at study entry

**Disease-free interval=days from the diagnosis of primary tumor to the diagnosis of initial metastasis

***time since initial metastasis=days from the initial diagnosis of metastatic disease to randomization date

Reviewer's comment:
Sentinel lesions are defined in the protocol as all measurable lesions existing at baseline that most clearly represent the state of disease in the clinical judgement of the investigator. The fact that among 129 patients with liver metastasis at study entry, 31 patients in the IL-2 (42%) arm and 13 patients on the histamine/IL-2 arm (24%) had 4 or more sentinel lesions at baseline, also suggests that patients on the IL-2 arm had a higher tumor load.

6.2.3. Concomitant therapy

According to the applicant, the case report forms did not capture all the subsequent therapies for patients after they discontinued study medications. Only antineoplastic therapies given within 28 days of the last dose of study medication were captured. FDA could not identify those patients who were treated with chemotherapy, immunotherapy or biochemotherapy from the submitted datasets. In the electronic dataset of nondrug therapy, FDA identified the following patients who received radiation or underwent surgical resection of tumor while on study:

Table 12: FDA Analysis of Radiation and Surgery Given within 28 days of the Last Dose of Study as in the Dataset nondrgtx_dvd

	ITT IL-2 N=153	ITT H/IL-2 N=152	ITT-LM* IL-2 N=74	ITT-LM* H/IL-2 N=55
Received radiation	10	9	5	2
Resection of tumor	3	3	1	1

*Patients with liver metastases at study entry

6.2.4. Efficacy results

6.2.4.1. Primary endpoints

The cut-off date for survival data was March 8, 2000. According to the applicant, the survival status of all patients was known on that cut-off date so there were no right censored subjects in the analyses. There were two primary analysis populations, i.e., ITT (all randomized patients) and ITT-LM (all patients who had liver metastasis at study entry). The applicant reported that in the ITT population, there was a trend for improved survival favoring the histamine/IL-2 treatment group, that did not reach statistical significance. In the ITT-LM subpopulation, the duration of survival for the patients in the

histamine/IL-2 arm was significantly longer than the survival in the IL-2 group (p=0.004).

Table 13: Applicant's Primary Analysis

	ITT IL-2 (N=153)	ITT H/IL-2 (N=152)	ITT-LM* IL-2 (N=74)	ITT-LM* H/IL-2 (N=55)
Survival (days)				
Median	245	272	154	283
95% CI	184-281	211 - 318	119 - 204	197 – 387
p-value**	0.1255		0.0040	

* Patients with liver metastases at study entry

**Unadjusted Log-rank Test of the Distribution Curves

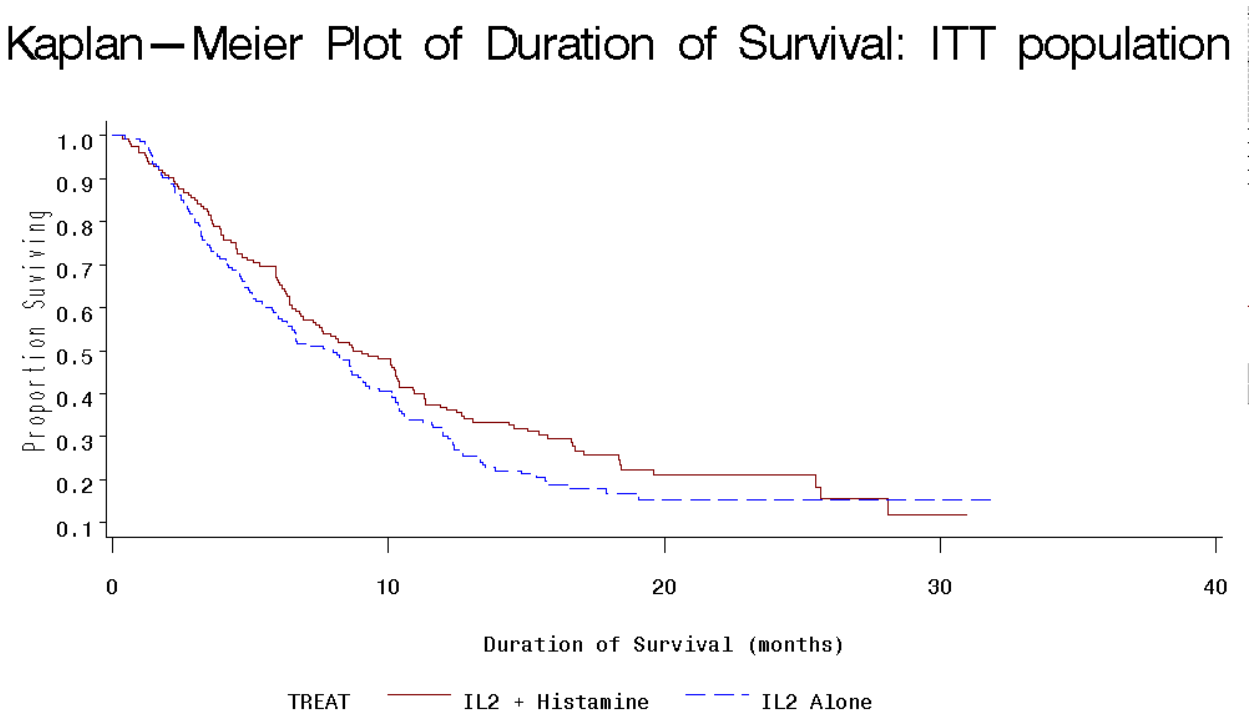

Figure 1: Survival curves of the ITT population of 305 patients (log rank P=0.1255)

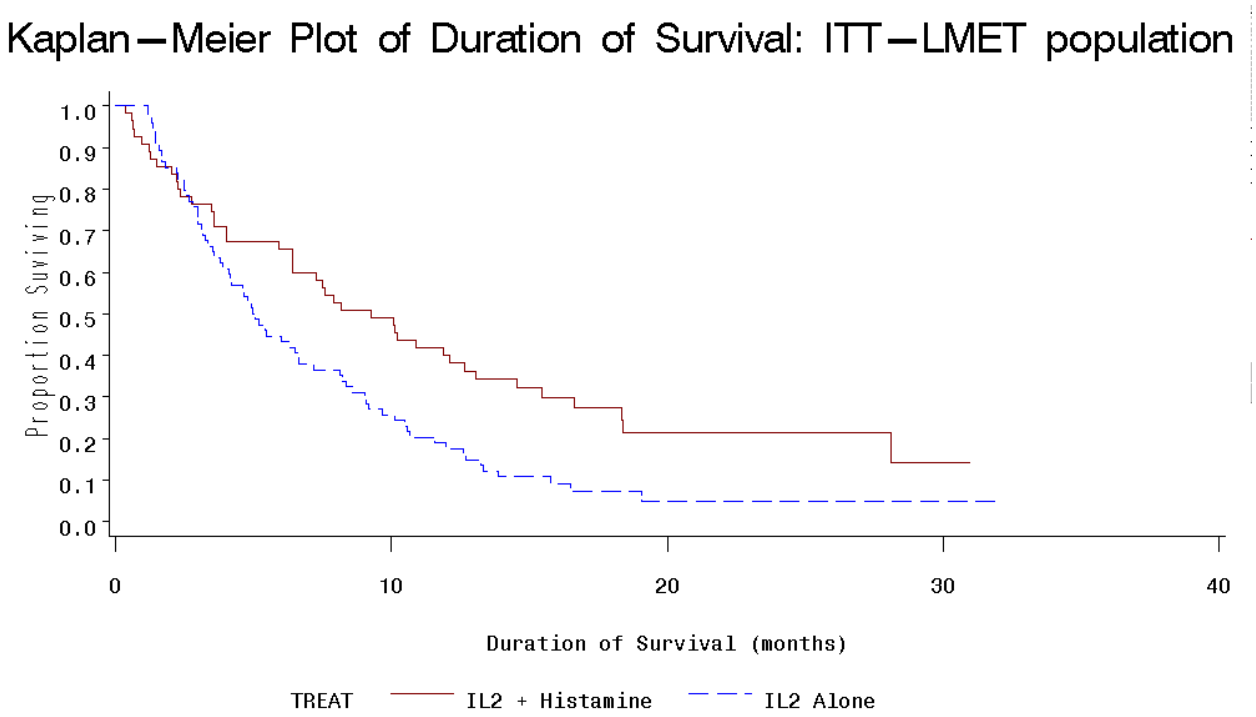

Figure 2: Survival curves of 129 patients with liver metastasis at study entry (log rank p=0.0040)

The FDA's analysis of the survival using the applicant's dataset confirmed the applicant's analysis. The applicant used 3/8/00 to calculate overall survival of all living patients. When FDA reviewers examined the submitted dataset, they found that the last visit date (i.e. date when patients were known to be alive or dead) was not 3/8/00 in 60 "living patients"
(26 on IL-2, 34 on histamine/IL-2). FDA has requested that the applicant submit evidence that these 60 patients were alive on 3/8/00.

The overall survival of patients who did not have liver metastasis at study entry (ITT-NO LMET) was longer in the IL-2 group (median: 10.3 months) than in the histamine/IL-2 group (median: 8.7 months), although the difference did not reach statistical significance (p=0.4493).

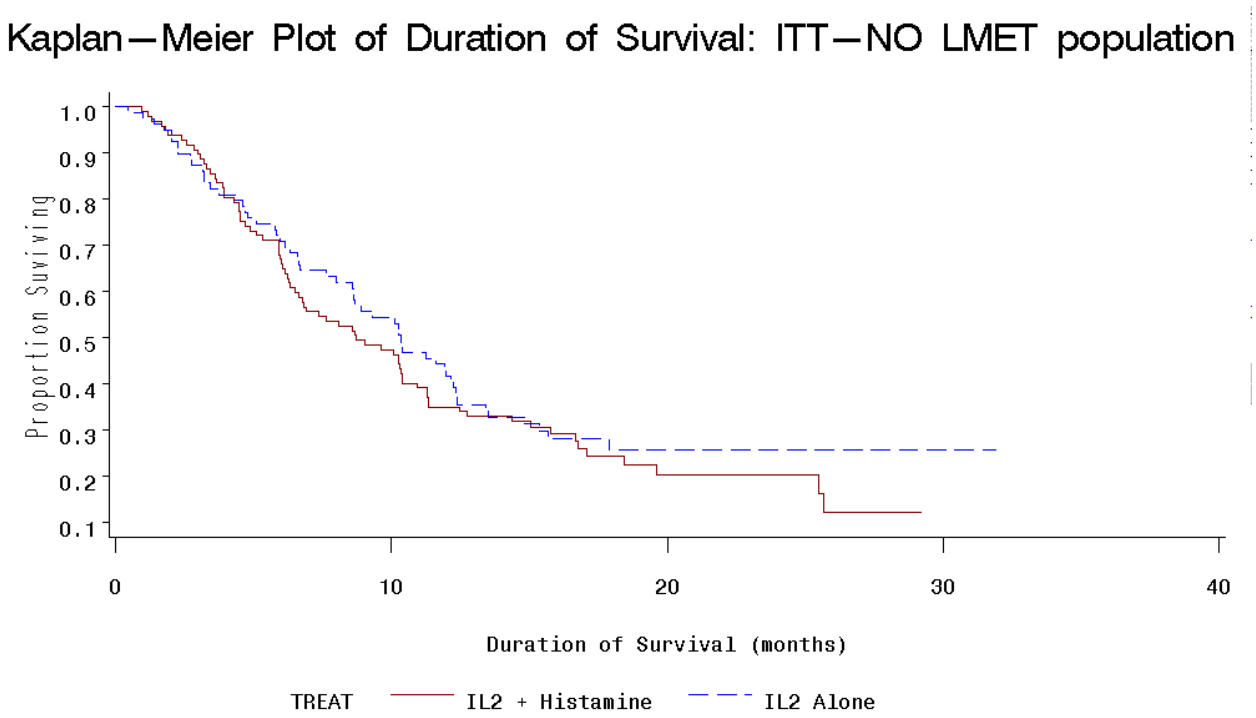

Figure3: Survival curves in 176 patients with no liver metastasis at study entry (log rank p=0.4493))

Reviewer's comment:
The applicant reported an updated survival analysis in the ODAC briefing document dated 11/8/00. The applicant has not submitted the updated survival data to FDA for review.

6.2.4.2. Adjusted analysis

In the final statistical analysis plan dated 11/18/99, the applicant stated that the following covariates would be used in the Cox models:

- Treatment (IL-2 vs. histamine/IL-2)
- Age
- Sex
- Race
- Number of prior anti-cancer therapies (none vs. more than one)
- Disease sites (skin/lymph/non-visceral, lung/GI/kidney/adrenal, liver/bone)
- Number of disease sites
- LDH
- Prior chemotherapy

- Baseline performance status
- Center (by geographic region-North, South, Mid-West, West).

According to the final statistical plan, these covariates would be explored separately using univariate models with treatment and covariate of interest at the 0.05 alpha level. Covariates would be explored in a multivariate manner using the automated backward selection method within the Cox model at the 0.05 alpha level with treatment and center, where applicable, retained in the same model.

Table 14: Applicant's Multivariate Analysis in the ITT population (N=305)

Covariates	Hazard Ratio	95% CI Hazard Ratio	Multivariate P-value
Age (≥65 vs. <65)	1.088	0.796-1.487	0.5974
Sex	1.626	1.208-2.189	0.0034
Race	0.536	0.255-1.126	0.0998
LDH (≥ ULN vs < ULN)	2.049	1.500-2.798	0.0001
Baseline Performance Status (1 vs 0)	2.100	1.554-2.838	0.0001
Geographic Region			
Mid-West vs South	1.213	0.743-1.978	0.4957
North vs South	0.857	0.527-1.394	0.6586
West vs South	0.731	0.469-1.139	0.2854
Disease sites			
Skin	1.371	0.977-1.923	0.0680
Lymph node	1.857	1.324-2.603	0.0003
Bone	2.840	1.746-4.617	0.0001
Lung	1.513	1.042-2.195	0.0293
Liver	1.416	1.016-1.975	0.0401
CNS	1.744	1.027-2.961	0.0397
Others	1.508	1.056-2.154	0.0239
Number of disease sites			
1 vs 2	1.872	0.935-3.746	0.0766
2 vs >2	1.482	0.913-2.405	0.1111
Number of disease sites (1 vs. more than one)	Not done	Not done	Not done
Disease Sites (nonvisceral vs. liver/bone vs. others)	Not done	Not done	Not done
Prior anti-cancer therapy	1.185	0.374-1.561	0.4602
Prior chemotherapy	1.185	0.854-1.645	0.3089
Treatment (histamine/IL-2 vs IL-2)	0.770	0.586-1.013	0.0612

Reviewer's comment:
The applicant's multivariate analysis did not include site of metastases (nonvisceral versus visceral), number of metastatic sites (1 vs. 2 or more), disease-free intervals from the primary tumor, and baseline albumin which were found to be independent prognostic factors for survival in metastatic melanoma (7, 8, 9, 10). Race and geographic region were not prognostic factors

in metastatic melanoma and it is unclear why these two covariates were included in the Cox model.

In the subgroup of patients with liver metastases at study entry (ITT-LM, N=129), there were many imbalances in patient characteristics as listed in Table 11 (age, sex, performance status, LDH, albumin, disease free interval, time since initial diagnosis of metastases, number of disease sites, and prior chemotherapy). The applicant performed a multivariate analysis of the relationship between pretreatment factors and treatment outcome using the Cox Proportional Hazard test.

Table 15: Applicant's Univariate and Multivariate Analysis in the ITT-LM population i.e. patients with liver metastases at study entry (N=129)

Covariates	Hazard Ratio	95% CI Hazard Ratio	Multivariate P-value
Age (≥65 vs. <65)	1.154	0.733-1.819	0.5364
Sex	1.203	0.769-1.884	0.4179
Race	0.698	0.200-2.445	0.5745
LDH (≥ ULN vs < ULN)	2.170	1.375-3.423	0.0001
Baseline Performance Status (1 vs 0)	2.953	1.656-4.061	0.0001
Geographic Region			
Mid-West vs South	1.180	0.519-2.684	0.6931
North vs South	1.150	0.525-2.520	0.7267
West vs South	1.028	0.502-2.101	0.9406
Disease sites			
Skin	1.452	0.839-2.512	0.1830
Lymph node	1.469	0.865-2.494	0.1549
Bone	5.795	2.682-12.519	0.0001
Lung	1.241	0.627-2.456	0.5358
CNS	1.330	0.557-3.174	0.5212
Others	1.058	0.630-1.778	0.8503
Number of disease sites			
1 vs 2	1.996	0.619-6.439	0.2475
2 vs >2	0.913	0.413-2.020	0.8222
Number of disease sites (1 vs. more than one)	Not done	Not done	Not done
Disease Sites (nonvisceral vs. liver/bone vs. others)	Not done	Not done	Not done
Prior anti-cancer therapy	0.319	0.100-1.017	0.0277
Prior chemotherapy	1.224	0.707-2.117	Not done
Treatment (Histamine+Il-2 vs IL-2)	0.463	0.286-0.750	0.0017

Based on these tests, the applicant concluded that the various imbalances did not have an impact on the statistical significance of the results for survival in ITT-LM.

Reviewer's comment:
The applicant's adjusted analysis did not include all the imbalances between the two treatment arms in the subpopulation of patients with liver metastases at study entry (ITT-LM). For example, disease-free interval, baseline albumin, and time since the diagnosis of the first metastasis. Disease-free intervals from the primary tumor and baseline albumin have been shown to be independent prognostic factors for survival (7, 9, 10).

FDA's adjusted analyses are based on imbalances in patient characteristics found by the FDA and the applicant as well as known prognostic factors in metastatic melanoma. It should be noted that the site and number of metastasis known to influence survival refers to the site and number of ***initial*** metastases according to the melanoma literature. The information on the initial site and number of metastases was not collected in this trial.

Because patient characteristics are mostly balanced in the ITT population, only adjusted analysis based prognostic factors was performed.

Table 16: FDA's adjusted analysis (ITT population) based on prognostic factors: N=305

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Histamine + IL-2 vs IL-2)	0.819	0.612, 1.096	0.1798
Liver metastasis (yes vs no)	1.030	0.761, 1.394	0.8480
Baseline Albumin	0.789	0.568, 1.096	0.1572
Baseline Performance Status (1 vs 0)	1.911	1.424, 2.565	0.0001
Log_eLDH	1.645	1.374, 1.968	0.0001
Prior chemotherapy (yes vs no)	1.060	0.777, 1.445	0.7128
Number of metastatic sites	1.163	1.070, 1.264	0.0004
Sex (Male vs Female)	0.717	0.542, 0.949	0.0199
Age Group (≥ 65 yrs vs < 65 yrs)	1.186	0.879, 1.600	0.2647
Disease-free survival since the initial diagnosis of primary tumor (< 1 yr vs ≥ 1 yr)	1.154	0.861, 1.545	0.3373
Skin/lymph node/lung only (yes vs no)	1.135	0.708, 1.819	0.5982

* P-value not adjusted for multiplicity.

Reviewer's comment:
It appears that treatment with the histamine/IL-2 combination does not have a significant impact on overall survival in the ITT population when the influences of prognostic factors are counted in the multivariate analysis.

When a similar adjusted analysis using prognostic factors was performed for the subgroup of patients with liver metastases at study entry (ITT-LM), the large treatment effect favoring the histamine/IL-2 combination diminished and the probability of false positive finding increased, raising the concern that the observed difference in survival could be due to the imbalances in prognostic factors between the two treatment arms.

Table 17: FDA's adjusted analysis (ITT-LM population) based on prognostic factors: N=129

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Histamine + IL-2 vs IL-2)	0.680	0.440, 1.041	**0.0806**
Baseline Albumin	0.718	0.432, 1.197	0.2053
Baseline Performance Status (1 vs 0)	2.074	1.310, 3.287	0.0020
Log_eLDH	1.586	1.234, 2.034	0.0002
Prior chemotherapy (yes vs no)	1.134	0.684, 1.896	0.6253
Number of metastatic sites	1.083	0.961, 1.221	0.1889
Sex (Male vs Female)	0.927	0.613, 1.391	0.7135
Age Group (≥ 65 yrs vs < 65 yrs)	1.371	0.887, 2.138	0.1616
Disease-free survival since the initial diagnosis of primary tumor (< 1 yr vs ≥ 1 yr)	0.677	0.427, 1.072	0.0950

Because the subpopulation of patients with liver metastases at study entry (N=129) was a **non-randomized** subgroup due to the lack of stratification for the presence and absence of liver metastases, there were differences in patient characteristics other than those known to have prognostic factors in metastatic melanoma. When all these imbalances (those found by the applicant and those found by the FDA) were used as covariates in the multivariate analysis, the treatment effect favoring the histamine/IL-2 combination diminished further.

Table 18: FDA's adjusted analysis (ITT-LM) based on imbalances in patient characteristics: N=129

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (Histamine+Il-2 vs IL-2)	0.700	0.447, 1.096	0.1193
Age Group (≥ 65 yrs vs < 65 yrs)	1.380	0.880, 2.164	0.1611
Sex (male vs female)	1.003	0.663, 1.516	0.9892
Baseline Performance Status (1 vs 0)	1.986	1.246, 3.167	0.0039
Number of metastatic sites	0.998	0.845, 1.178	0.9814
Log_eLDH	1.687	1.298, 2.192	0.0001
Lymph node (yes vs no)	1.672	1.035, 2.072	0.0356
Lung (yes vs no)	1.167	0.701, 1.942	0.5529
CNS (yes vs no)	1.065	0.457, 2.484	0.8845
Prior Chemotherapy	1.249	0.733, 2.129	0.4126
Disease-free Survival since the initial diagnosis of the primary tumor (≥ 1 yr vs < 1 yr)	0.609	0.378, 0.981	0.0415
Baseline Albumin	0.760	0.456, 1.267	0.2929
Time from initial met to randomization (≥ 1 yr vs < 1 yr)	0.816	0.470, 1.414	0.4680

* P-value not adjusted for multiplicity

6.2.4.3. Secondary endpoints

Secondary endpoints included tumor response rate and time to tumor progression (TTP). According to the applicant, "first progression" was captured as the number of days from randomization to the first observed progressive disease or death due to melanoma after Week 12. "Last progression" was the date of the last observed progressive disease, or death due to melanoma after Week 12. It should be noted that patients who died from causes other than melanoma are excluded from this analysis. The applicant found a significant difference in favor of histamine/IL-2 for both time to "first progression" (p=0.0375) and time to "last progression" (p=0.014).

Table 19: Applicant's Analysis of Time to Progression

	ITT IL-2 (N=153)	ITT H/IL-2 (N=152)	ITT-LM* IL-2 (N=74)	ITT-LM* H/IL-2 (N=55)
Time to First Progression				
Median (days)	86	89	84	85
95% CI	84-88	86-92	82-86	84-90
p-value	0.0375		0.0074	
Time to last progression				
Median (days)	100	131	87	128
95% CI	87-126	113-144	83-103	89-169
p-value	0.0104		0.0033	

*Patients with liver metastases at study entry

Reviewer's comment:
The clinical significance of time to last progression is unclear in view that the patient has already progressed. The applicant's methodology for calculating time to tumor progression was inaccurate. As FDA has previously indicated to the applicant, death is not equal to tumor progression unless progression is documented around the time of death. Patients who died without documented tumor progression should be censored on the last day when the disease was measured and assessed. In addition, the FDA found in its preliminary analysis that 62 patients (34 on IL-2, 28 on histamine/IL-2) had no appropriate follow-up scans to assess tumor progression. FDA assessment of time to tumor progression is ongoing.
The overall response rate in the entire study population was 3%, equally distributed on both treatment arms. Only 3 complete responses (CRs) were observed, and none of the CRs occurred in patients with liver metastases.

Table 20: Applicant's Analysis of Tumor Response

	Number patients			
	ITT IL-2 (N=153)	ITT H/IL-2 (N=152)	ITT-LM IL-2 (N=74)	ITT-LM H/IL-2 (N=55)
CR	2	1	0	0
PR	3	4	0	2

CR + PR	5	5	0	2

Reviewer's comment:
Only two of these ten responders were in the ITT-LM (the subgroup of patients with liver metastases at study entry) and both were on histamine/IL-2 arm. The two responses are described below:

0005000006: One liver lesion decreased from 1.4cm x 2.3 cm to 1.5 cm x 1.5 cm.

0065000003: Patient had numerous liver lesions. Only two liver lesions were chosen as sentinel lesions (2.5 cm x 2.7 cm and 2.5 x 3 cm decreasing to 1cm x 0.7 cm and 1 cm x 1.2 cm).

According to FDA assessment, the patient with CR on histamine/IL-2 (0005000021) had residual tumor on the last scan in the submitted database. The applicant stated that a PET scan performed at the end of 8 cycles was normal but no CT of Chest was performed. Of note, the patient did not have a PET can at baseline.

Table 21: FDA Analysis of the responders

CASE_ID	Rx	Resp	Measurable Disease Used to Assess Resp	Non-measurable Disease at baseline (not used to assess response)
0003000007	H/IL-2	PR	Paravertebral mass	Many lung nodules
0005000006	H/IL-2	PR	Lung, liver	L-hilar mass
0005000021	H/IL-2	CR	R subcarinal mass	None
0012000004	H/IL-2	PR	Lung nodules	Bilat lung nodules
0013000003	IL-2	PR	Lung lymph nodes	Bilat mediastinal and hilar lymph nodes
0015000009	IL-2	PR	R axillary Lymph node, lung lymph node	None
0016000001	IL-2	PR	Pelvic lymph nodes, lung lesion	None
0020000001	IL-2	CR	Cervical lymph node	None
0065000003	H/IL-2	PR	Liver lesions	Numerous liver lesions
0082000002	IL-2	CR	Neck lymph nodes	None

FDA's assessment of response duration is based on the submitted electronic dataset containing the dates of follow-up imaging studies. FDA calculated response duration using the first day when response was observed and the last day when the patient was assessed by appropriate imaging studies.

Table 22: Comparison of Response Duration Calculated by FDA and the Applicant

CASE_ID	Rx Arms	Resp	Response Date	Last Scan Date	Response Duration (days)	
					FDA	Applicant
0003000007	H/IL-2	PR	3/25/99	3/24/99	0	350
0005000006	H/IL-2	PR	5/11/98	12/7/98	210	214
0005000021	H/IL-2	CR	8/24/99	8/24/99	0	94
0012000004	H/IL-2	PR	6/17/98	1/5/99	202	209
0013000003	IL-2	PR	1/13/98	9/16/98	246	786
0015000009	IL-2	PR	1/25/99	8/24/99	211	409
0016000001	IL-2	PR	10/6/97	6/29/98	266	885
0020000001	IL-2	CR	6/5/98	10/7/98	124	125
0065000003	H/IL-2	PR	2/16/99	5/7/99	80	81
0082000002	IL-2	CR	9/3/98	9/3/98	0	248

6.2.4.4. Quality of life findings

FDA Analysis of quality-life data is ongoing

6.2.4.5. Summary of efficacy results

The applicant: Study MP-US-M01 suggested that advanced melanoma patients with liver involvement who were treated with histamine/IL-2 had a clinically meaningful and statistically significant benefit in survival, time-to-disease progression, and quality-of-life adjusted survival over those treated with IL-2 alone. Statistically significant differences in time to “first ”and “last ”progression were demonstrated in both the ITT and ITT-LM populations. The applicant believed that these were important surrogate endpoints because they provided a real clinical benefit to the patient and further supported the improved overall outcomes for patients treated with histamine/IL-2.

FDA: The substantial variability in survival of patients with advanced melanoma has been well documented in the literature. In studies analyzing the prognoses of patients with distant metastases using Cox regression analysis, the first site of metastases, the number of first metastatic sites, and elevated LDH were the most predictive of poor survival. Two studies have shown that liver involvement did not consistently predict poor survival, suggesting that survival of patients with liver metastasis may be influenced by other prognostic factors.

Study MP-US-M01 was not stratified by any known prognostic factors in metastatic melanoma. The differences in median survival between the two treatment arms in the ITT population (N=305) was one month, favoring the histamine/IL-2 arm, but this did not reach statistical significance (p=0.1255). There was an apparent difference in survival between the treatment arms in the subpopulation of patients who had liver metastasis at study entry (N=129) favoring the histamine/IL-2 arm. The difference of 4.2 months in median survival was statistically significant (p=0.0040). In the subpopulation of patients with no liver metastasis at study entry (N=176), the difference in survival between the two treatment arms was 1.6 months, favoring the IL-2 arm, but did not reach statistical significance (p=0.4493). The apparent survival difference in the subpopulation of patients with liver metastasis at study entry should be interpreted with caution because it is a non-randomized subgroup due to the lack of stratification for the presence or absence of liver

metastases. This resulted in many imbalances in patient characteristics that could have affected the survival. For example, more patients on the histamine/IL-2 arm had liver only metastases, fewer sentinel lesions identified at baseline, better performance status, longer disease free interval from the diagnosis of primary tumor and more had lived ≥1 year from the first diagnosis of metastasis. There was no evidence that the histamine/IL-2 combination had any anti-tumor activity as measured by response rate and the analysis of time to tumor progression data was problematic due to the missing follow-up scans. Furthermore, the protocol required a minimum of one sentinel lesion be followed and by the FDA's analysis, the median number of sentinel lesions identified at baseline was 2 in both treatment groups. In patients with multiple sites of metastatic disease, changes in a few sentinel lesions may not reliably represent changes in the overall disease state.

6.2.5. Safety results

Patient disposition:

Table 23: Applicant's Analysis of Patient Disposition on MP-US-M01

Patient Disposition	IL-2 N (%)	H/IL-2 N (%)
Randomized	153	152
Received at least one dose	152 (99)	151(99)
Completed 1 Cycle of treatment	119 (78)	119 (78)
Completed 8 Cycles of treatment	10 (7)	12 (8)
Entered extension study	6 (4)	6 (4)
Discontinued (Primary Reason)		
Death	3 (2)	3 (2)
Progressive disease	109 (71)	110 (72)
Toxicity	5 (3)	4 (3)
Adverse Event/Intercurrent illness	9 (6)	10 (7)
Non-compliance	3 (2)	3 (2)
Other	14 (9)	10 (7)

FDA's analysis of patient disposition was derived from two submitted datasets i.e., csum_dvd and stdycomp_dvd.

Table 24: FDA's Analysis of Patient Disposition

	ITT IL-2 N=153(%)	ITT H/IL-2 N=152 (%)	ITT-LM IL-2 N=74 (%)	ITT-LM H/IL-2 N=55 (%)
Received only 1 Cycle	33 (22)	32 (21)	19 (26)	16 (**29**)
Received ≥2 Cycles	119 (78)	119 (78)	54 (73)	38 (69)
Received 8 cycles	10 (7)	12 (8)	3 (4)	4 (7)
Withdrawal	143	140	71	51
Death	3	3	**0**	**2**
Progression	109	110	56	38
AE	20	16	10	6
Non-compliance	3	3	2	1
Ineligible	1	1	1	1
Withdrew consent	6	7	1	3
Unknown	1	0	1	0

Reviewer's comment:
Among 65 patients who only received one cycle of therapy, 33 withdrew due to progression of disease as per the applicant (17 on IL-2, 16 on histamine/IL-2), 4 died (1 on IL-2, 3 on histamine), and 17 withdrew due to adverse events (9 on IL-2, 8 on histamine/IL-2). Among 33 patients who withdrew due to progression of disease as per the applicant, FDA could not find follow-up scans documenting tumor progression in 16 patients (7 on IL-2 arm, 9 on histamine/IL-2). Interestingly, among these 65 patients, 18 lived more than 6 months (8 on IL-2, 10 on histamine/IL-2), 8 lived more than 12 months (2 on IL-2, 6 on histamine), 3 were alive at the cut-off date of 3/8/00 (all on histamine/IL-2 arm). Two of these 3 long-term survivors on histamine/IL-2 withdrew from the study due to progression of disease as per the applicant. The long survival of these three patients who received only 4 weeks of histamine/IL-2 seems more likely due to the indolent nature of their disease rather than the treatment effect of histamine/IL-2.

Dose Reductions:

It appeared that dose reduction of histamine was not captured on the case report form.

FDA assessment of dose reduction is ongoing.

Applicant's analysis of safety (NDA Desk copy volume 2.22): Cardiovascular adverse events were reported in > 90% of the study population and included hypotension, pallor, palpitation, tachycardia and vasodilation (label). Most adverse events were of mild or moderate severity, and the differences in incidence between treatment groups were due primarily to the expected physiological effects of histamine therapy. Patients in the histamine/IL-2 group had a higher incidence of adverse events affecting the cardiovascular system (hypotension, palpitation, tachycardia, and vasodilation, and the associated nervous system event of dizziness) and those related to injection site reactions. The majority of these events were mild or moderate in severity, considered related to study drug, and did not result in modification of study drug administration. The incidence of adverse events did not increase over the course of the study, suggesting that histamine is a drug that can be tolerated in long-term usage. A total of 63 SAEs were reported in the IL-2 group compared to 54 SAEs in the histamine/IL-2 group. Most of AEs were considered unrelated to study drug (55/63 i.e., 87% in the IL-2 group; 40/54, 74% in the histamine/IL-2 group). A total of 4 patients in the IL-2 group and 7 patients on the histamine/IL-2 group died of causes other than melanoma during the study or in the 28 day period following study discontinuation. Three deaths were considered related to study drugs and all three patients were treated with histamine/IL-2.

The FDA's analysis of safety data was based on the adverse event dataset submitted by the applicant. Among 305 patients on study, 174 patients (57%) suffered at least one grade 3 or grade 4 adverse event (92 on IL-2, 82 on histamine/IL-2). Specific types of grade 3 or 4 toxicities are listed in Table 25.

Table 25: Number of Patients Who Experienced at Least One of the Listed Toxicities

	ITT IL-2 N=153(%)	ITT H/IL-2 (N=152)	ITT-LM IL-2 (N=74)	ITT-LM H/IL-2 (N=55)
Grade 3	90 (59%)	79 (52%)	49 (66%)	31(56%)
Headache	3 (2%)	11 (7%)	0 (0%)	6 (**11%**)
Flushing	2	3	0	1
Hypotension	1	1	1	0
Pruritis	2	3	1	1
Pain	9 (6%)	12 (8%)	7 (9%)	4 (7%)
Chest pain	5	4	3	1
CHF	2	0	1	0
Nausea	11 (7%)	8 (5%)	9 (12%)	4 (7%)
Vomiting	7 (5%)	9 (6%)	6 (8%)	4 (7%)
Anorexia	9 (6%)	3	2	0
Dyspepsia	0	1	0	0
↑LFT	0	3	0	**2**
↑Bilirubin	4	2	4	2
Liver failure	0	1	0	**1**
Coma	2	2	0	0
Mental status change	7 (5%)	5	4	2
Dyspnea	10 (7%)	8 (5%)	7 (9%)	2 (4%)
Edema/ascites	16 (10%)	9 (6%)	7 (9%)	6 (11%)
Asthenia/malaise	19 (12%)	18 (12%)	8 (11%)	7 (13%)
Grade 4	**8 (5%)**	**10 (7%)**	1 (**1%**)	4 (**7%**)
Dyspnea	2	1	0	0
Hypotension	1	1	0	0
Syncope	1	2	0	0
Cardiac arrest	1	0	0	0
CHF	0	**2**	**0 (0%)**	**1 (2%)**
Acute MI	0	**1**	0	**1**
Dehydration	1	0	1	0
Pain	1	0	0	0
UGI bleed	1	1	0	0
Subarachnoid bleed	0	1	0	1
Seizure	0	1	0	0
Liver failure	0	**2**	**0 (0%)**	**2 (4%)**
Ascites	1	**0**	**1**	**0**
Death Within 28 days of last dose of study medication	**13 (8%)**	**17* (11%)**	**8 (11%)**	**10**(18%)**

*Two patients who died within 28 days of last dose was not included in the applicant's electronic tabulation of deaths within 28 days of last dose (Pt. 002-002 and Pt. 014-009).
**Pt. 014-009 who died within 28 days of last dose was not included in the applicant's electronic tabulation of deaths within 28 days of last dose.

FDA review of narratives and CRFs on 30 patients who died within 28 days from the last dose of study medication are ongoing:

Three deaths on the histamine + IL-2 arm were associated with SAE's linked to study drugs by the applicant – Pt. M01-002-002 (lethargy and unresponsive associated with myocardial and cerebral infarctions, both considered probably related to study drugs), Pt. M01-029-001 (seizure considered probably related) and Pt. M01-115-005 (Liver failure considered by investigator related to IL-2).

The preliminary FDA review of narratives and CRF's of 10 patients are summarized below:

Pt. M01-002-002 (histamine/IL-2) – 50 yrs female randomized on 4/15/98 had lung and lymph node metastases. She had a history of multiple prior therapies, including polyvalent melanoma antigen vaccine-low dose IL-2 encapsulated liposomes from 7/10/95 to 6/96. She had a history of excision of a metastatic lesion from the right cerebellum 10/30/96 and whole brain radiotherapy in 11/96. At baseline she had mild renal insufficiency (creatinine=1.7) and a right bundle branch block. First dose was administered on 4/20/98. Subsequent doses included 4/28 and 4/29. Last dose was given on 5/5 (IL-2) and 5/6 (histamine). On 4/28 grade 2 lethargy was recorded as an AE, and on 4/29 Grade 3 lethargy was recorded. On May 7 the patient was removed from study, and the CRF indicates the patient had double vision and grade 3 unresponsiveness. Vancomycin and ceftazadime were started that day. The narrative indicates that MRI, echocardiogram, ECG, and CPK MB subfraction indicated that the patient had had both a MI and cerebral infarction. MRI of brain on 5/9 was recorded to have shown extensive diffuse abnormality in the frontal, parietal, and occipital lobes consistent with infarct. The patient died on 5/24/98. **According to the study report, this patient's death was related to study drug**. Her baseline PS=1, but her baseline QoL questionnaire indicated that she spent most of the day in bed or in a chair, that she had impaired activity level, and difficulty walking, though she needed no assistance with activities of daily living.

Pt. M01-013-011 (histamine/IL-2) – 53 yo male with history of ocular melanoma entered the study on 6/25/98 with liver metastases. His previous treatment included liver embolization 6/16/98. He had a history of hypercholesterolemia, hypertension, peripheral neuropathy, and hepatomegaly. Baseline laboratory tests included Bili = 0.6, AST=45,

Alkaline phosphatase=278, and LDH=779. Treatment started on 6/30/98 and the last dose was administered on 7/15/98. On 7/21 the AE sheet in the CRF states that the patient had grade 2 jaundice. On July 27 grade 3 elevation of bilirubin was reported, but laboratory values were not reported. The narrative submitted for this patient indicates that PD was noted on 7/31/98, but no documentation was provided in the CRF. This patient died on 8/2/98 with "liver failure". This patient reportedly had extensive replacement of the liver with tumor and death probably was related to PD, however the rapid deterioration could have been related to toxicity.

Pt. M01-014-001 (histamine/IL-2) – 62 yo male randomized on on 6/26/98. Metastatic sites included liver, spleen, lymph node, lung, skin. He had baseline hepatomegaly and abdominal discomfort in the RUQ. Baseline PS=1. Initial dose was administered 7/1/98. Last dose was administered 7/14. PS declined to 2 on 7/7/98 and further to 4 on 7/14/00. His baseline Bili=1.0, AST=65, alkaline phosphatase=265. CRF indicates dosing was interrupted 7/10 (grade 3 jaundice, grade 2 fatigue/lethargy) and 7/13 (confusion). On 7/7 there was an AE for grade 3 elevation of alkaline phosphatase (644). On 7/14 an AE for grade 4 elevation of LFT's was recorded. Study participation was discontinued on 7/16 for withdrawn consent for liver failure ("unrelated" to study treatment). The patient died that day. This event could have been due to disease progression, but toxicity related death couldn't be excluded.

Pt. M01-027-004 (histamine/IL-2) – 74 yo male randomized on 7/2/98, had a history of ocular melanoma and had liver metastases. He had hepatomegaly and RLE edema at study entry. Baseline Bili=1.2, AST=121, alkaline phosphatase=248, LDH=1739, albumin = 3.3, Platelets=98K. Baseline PS was 0. First dose was administered on 7/9/98 and last dose on 7/10/98. AE's recorded on 7/9 include nausea, dry heaves (grade 2) and increased edema (grade 3). On 7/14 study participation was ended due to PD, which is not documented in the CRF. On 7/17 changes in the physical examination noted in the CRF include increased edema and hepatomegaly. The patient died on 7/20/98. Given the patient's baseline laboratory results and the reported increased hepatomegaly on physical examination, this patient's death probably was due to PD, although it is possible that the patient died from toxicity.

Pt. M01-029-001 (histamine/IL-2) – 68 yo male randomized on 4/9/98 had metastases to lung and sacrum. History included rheumatoid arthritis, hyperglycemia (glucose=240), anemia, and abdominal pain. Baseline medications included hydrocortisone (10 mg/5 mg) substituted for the prednisone 5 mg/day he had been on for arthritis. Baseline PS=0. Initial dose was administered on 4/14/98. His last dose was on 5/8/98. On 5/8 he was

believed to have had a seizure when his "eyes rolled up", he became ashen, and his blood pressure was unobtainable. This event was considered related to study drugs. He died on 5/8. Prior AE's included weakness and inability to get out of bathtub on 4/15 (day of drug administration) and grade 2 diarrhea 4/28 (day of histamine administration and 3 days after a dose of IL-2). This patient's death is considered study drug related in the applicant's Study Report Table 29.

Pt. M01-108-003 (histamine/IL-2) – 39 yo female randomized on 9/10/98. She had metastases to liver, spleen, lung, bones, adrenal gland, omentum, lymph nodes, skin. Her medical history included dyspnea, ascites, lower extremity edema, back pain, fatigue, vomiting, fever. Hydrocortisone replacement therapy was not included in her medication list. Her baseline PS=1. Initial dose was 9/14/98. Last dose was 9/29/98. Laboratory tests in the interim revealed a serum sodium of 116 on 9/18 (2 days after a dose of histamine). Baseline serum sodium was 133 (potassium 4.0). AE's included grade 2 dyspnea on exertion on the first day of treatment, grade 2 dehydration and serum sodium=114 (potassium = 5.7) on 10/2, grade 2 elevation of BUN and grade 4 hyponatremia on 10/4, grade 3 weakness, grade 3 hyponatremia, grade 3 acute abdominal pain, and grade 2 decrease in respiratory effort on 10/5. On 10/6 grade 3 hypocalcemia was recorded. She was reported to have PD on 10/5 in the narrative. Supplemental oxygen was initiated on 10/3. She was discontinued from study on 10/8 and died. This patient probably died of disease progression, but contribution of study drug cannot be excluded. She indicated in her baseline QoL questionnaire that she spent most of her day in bed/chair, had problems walking, problems with mobility and an impaired activity level. She denied needing assistance with ADL's. She rated her baseline health a 20 on a scale of 0-100, with zero equal to worst possible health.

Pt. M01-115-005 (histamine/IL-2) – 34 yo female randomized on 2/11/99 (consent obtained over the telephone). She had metastatic involvement of liver and lymph nodes. Medical history included dyspnea, pneumonia, weakness, abdominal pain. Her medications included cephalexin for pneumonia. Her baseline Bili<0.1, AST=83, alkaline phosphatase= 132, and LDH=1775. PS=0. First dose was administered on 2/15/99. The last administration of IL-2 was 2/16/99. Maxamine was administered from 2/15 to 2/19 (a single dose), then stopped. The narrative indicates that the patient became progressively weaker and more dehydrated from nausea, diarrhea, and fever. On 2/19 AE's for grade 4 mental status change, grade 4 liver failure (no laboratory results documented in CRF), grade 3 nausea, grade 3 tachypnea, and grade 4 sepsis were recorded. The liver failure was attributed to study drugs. She died on 2/21/99. In her baseline QoL questionnaire this

patient indicated that she spent most of the day in bed/chair, had trouble walking, was in a wheel chair 3 days prior, had impaired activity, but needed no assistance with her ADL's. She rated her health a 0, the worst possible rating.

Pt. M01-008-008 (IL-2) – 66 yo male randomized on 11/24/97. This patient had liver, lung, and lymph node metastases. His medical history included "labile hypertension", dyspnea, orthopnea, cough, ventricular ectopy, RLE edema. PS=1. First dose was administered on 11/25/97. The only subsequent doses were administered and recorded in CRF were 11/26, 12/8 (single dose), and 12/9 (single dose). PS was recorded as 1 on 12/8. On 12/31 an AE of respiratory infection was recorded. The patient was hospitalized from 1/2/98 to 1/7/98 for influenza. He died 1/7/98 after being removed from the study on 1/5/98. In this patient's baseline QoL assessment he indicated that he spent most of the day in a bed or chair, but that he had no impairment of activity and needed no assistance with ADL's. This patient's death was probably secondary to infection, though contribution of study drug to this event cannot be completely excluded.

Pt. M01-012-012 (IL-2)– 49 yo male randomized on 2/2/98 with a history of an esophageal primary malignant melanoma. At study entry he had lung metastases and a soft tissue mass of the stomach. He had a history of GI bleed. His prior treatment included IL-2 from 10/7/97 to 12/5/97. Baseline PS was 0. The initial dose of IL-2 was administered on 2/2/98. The CRF indicates doses were also administered on 2/3, 2/9 and 2/16. On 2/16/98 grade 4 syncope, grade 4 dyspnea, cardiopulmonary arrest, and upper GI bleed were recorded. The patient died that day. The events were not considered related to study drug. The patient did have a gastric mass that was likely the source of the GI bleed, but no details were provided to allow excluding the cardiopulmonary arrest and dyspnea were related to study drug instead of GI bleed.

Pt. M01-012-017 (IL-2**)** – 68 yo male randomized on 3/23/98. At study entry he had lung and lymph node metastases and a soft tissue mass. He had a history of Whipple surgery (3/5/97), left nephrectomy (1/6/98), CABG, HTN, GI bleed, SBO. Baseline PS was 1. He started treatment on 3/23/98 and was last treated on 4/7/98. He was removed from study for PD on 4/13/98, but no documentation of the PD appears in the CRF. His PS on 3/30 had declined to PS=2. AE's recorded include confusion (3/25-4/6), diarrhea (3/26-4/4), fever (3/23-4/4), hypotension 3/30-4/7), diaphoresis (3/30-4/6), fatigue (4/6-4/22; study drug interrupted for this AE), lethargy (4/6-4/17; study drug interrupted for this AE). On 4/15 the CRF indicates that the patient experienced edema, lethargy, hallucinations, and arrhythmia. Supplemental O2 was started 4/17. The patient was hospitalized on 4/15/98 and died 4/22. Medications included

vancomycin, ciprofloxacin, erythromcyin, clindamycin. This patient's death was attributed to melanoma. The clinical picture derived from the CRF could also be consistent with IL-2 toxicity.

FDA summary of safety analysis:
It appeared that a significant number of patients on this study suffered grade 3 or 4 adverse event (58%). In the absence of a control arm with no IL-2, it is not possible to determine how many of these grade 3-4 toxicities are due to the underlying disease. In the recently published randomized trial of temozolomide versus dacarbazine, the percentage of patients reporting grade 3 or 4 adverse events was 36-38%. Except for grade 3 headache, there was no significant difference in grade 3-4 adverse events between the two treatment arms. This raises a concern that the IL-2 regimen used in MP-US-M01 may not be a well tolerated outpatient regime as the applicant has claimed.

7. Supportive Study

The only other study used the same dose and schedule of IL-2 and histamine in metastatic melanoma is Study MP-MA 0103. This is an ongoing multi-center, open-label, single arm study in adult patients with measurable metastatic melanoma. Patients may be previously untreated or may have received chemotherapy, gene therapy with IL-2 transduction, radiation therapy, vaccine immunotherapy with IL-2 or interferon. A total of 100 patients are planned to be enrolled into the study at seven centers in the United States. The primary measures of clinical efficacy are time to progression and survival. The secondary measures of clinical efficacy are tumor response rate and duration of response. The study is also designed to evaluate the role of IL-2 and histamine in regulating immune system.

In the NDA, the applicant submitted the survival data of 39 patients and safety data of 35 patients. Table 26 listed the applicant's analysis.

Table 26: The Applicant's Analysis of Efficacy and Safety of MP-MA-0103

	All Patients N=39	Patients with liver met N=10
Survival (mean)	231 days	231 days
TTP	Not provided	Not provided
Response rate	Not provided	Not provided
Death	16	5
Grade 3 toxicity	Not provided	Not provided
Grade 4 toxicity	Not provided	Not provided
Serious Adverse events	7	Not provided
Pleural effusion	1	
Tachypnea	1	
Tachycardia	1	
Fatigue/weakness	1	
Upper GI bleed	1	
DVT, Cord compression	1	
Brain metastasis	1	

Reviewer's comment:
As FDA previously indicated to the applicant, this single arm study would not directly address whether use of histamine added benefit to IL-2 without a control arm. In open-label trials, objective tumor response rate and response duration were efficacy endpoints that could be most reliably measured. Time to disease progression and survival should be evaluated but are outcomes difficult to interpret in the absence of a control arm. Study MP-MA-0103 could only provide safety data and would not impact efficacy claims. DODP will be conducting a safety review of this study using data in the safety update to be submitted by the applicant in the next few weeks.

8. Overall Summary

Study MP-US-M01 is a randomized multi-center, open-labeled study designed to demonstrate the added benefit of histamine to IL-2 in the treatment of metastatic melanoma. 305 patients were enrolled in the study. No stratifications of prognostic factors were performed and the efficacy and tolerability of the treatment regimen used in the study have never been demonstrated in a pilot study. The primary efficacy endpoint is survival. Based on efficacy results in a subgroup of 129 patients who were found to have liver metastases by imaging studies at study entry, the applicant is seeking the following indication:

Histamine dihydrochloride is indicated for adjunctive use with interleukin-2 in the treatment of adult patients with advanced metastatic melanoma that has metastasized to the liver.

The following table summarizes the FDA's analysis of efficacy and safety from study MP-US-M01:

	ITT IL-2 (N=153)	ITT H/IL-2 (N=152)	ITT-LM* IL-2 (N=74)	ITT-LM* H/IL-2 (N=55)
Survival (days)				
Median	245	272	154	283
95% CI	184-281	211 - 318	119 - 204	197 – 387
p-value	0.1255		0.0040	
Response Rate	3%	3%	0%	4%
Time to progression	Pending	Pending	Pending	Pending
Withdrawal**	143	140	71	51
Death	3	3	**0**	**2**
Progression	109	110	56	38
AE	20	16	10	6
Death within 28 days of study med	13 (8%)	17 (11%)	8 (11%)	10 (**18%**)
Grade 4 toxicity	8 (5%)	10 (7%)	1 (1%)	4 (7%)
Grade 3 toxicity	90 (59%)	79 (52%)	49 (66%)	31 (56%)

*Patients with liver metastases at study entry

**Reasons for withdrawal as per the applicant

Metastatic melanoma is known to have a variable clinical course influenced by prognostic factors. FDA analysis of the distribution of known prognostic factors in metastatic melanoma found many imbalances between the two treatment arms in patients with liver metastases. These included performance status, albumin, disease-free interval, and number of metastatic sites. These imbalances consistently favored the histamine/IL-2 arm. This raises a concern that the apparent survival difference in this subgroup may be attributed to patient selection and the natural history of the disease.

FDA safety review found that the death rate within 28 days of the last dose of study medication was as high as 18% in the 55 patients with liver metastases who received the combination of histamine/IL-2. The incidence of grade 3-4 toxicities is 58% in the entire study population (N=305) and 62% in patients with liver metastases (N=129). In the absence of a control arm with no IL-2, it is not possible to determine how many of these deaths and grade 3-4 toxicities are due to the underlying disease. In the recently published randomized trial of temozolomide versus dacarbazine (N=305), the percentage of patients reporting grade 3 or 4 adverse events was 36-38% and 24 deaths occurred during treatment (8%). The applicant did not perform an analysis of dose reduction and treatment delays.

Issues for discussion at ODAC: The proposed indication of histamine plus IL-2 is for patients with melanoma metastasized to liver.

1) In the subgroup of patients with liver metastases, there are many imbalances in prognostic factors between the two treatment arms. Does the apparent survival difference in this subgroup of patients in a single trial represent persuasive evidence of treatment efficacy?

2) The administration of this IL-2 regimen with or without histamine is associated with significant toxicities. The incidence of grade 3-4 toxicities is 58% in the entire study population (N=305) and 62% in patients with liver metastases (N=129). Among the 129 patients with liver metastases at study entry, 18 died within 28 days of the last dose of study medication. Given the observed toxicity data, is this treatment a safe and tolerable regimen in patients with liver metastases?

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