

Whether actually the presence of liposomes is mandatory has not been investigated or described. Clearly, NMR spectroscopy cannot differentiate whether a signal comes from a gas substance 1) dispersed in solution, 2) encapsulated in a lipid particle as gas, or 3) dispersed in solution, which is encapsulated in a lipid particle.

No necessity for particles

Regardless, the Sponsor concluded, in the next sentence, without presenting any evidence that "... the increase in signal in the presence of lipid suggests that the lipid blend is essential in the formation and stabilization of the gas in the **activated DMP 115 Solution.**" However, this in itself does not necessarily mean that liposomes are present.

Phospholipids slow down dissipation of PFP from the drug blend

Thus, it transpires that the inclusion of phospholipids into the formulation slows down dissipation of gaseous PFP from solution, which may be even prolonged by emulsification of the formulation by shaking, referred to in this NDA submission as "activation". The introduction of **phospholipids** into the formulation **is not absolutely necessary for the detection of the PFP gas in the formulation**, it only increases its detected amount. Whether the time interval from activation to eventual injection is of essence in this process, or not, was not measured by NMR spectroscopy, or described.

Drug composed of liposomes of variable size, determined visually as well as by any other means

Before turning to a detailed discussion of the safety profile of the drug, what remains to be clarified is the the second part of the Sponsor's introductory sentence and, therefore, the main information about the nature of the drug formulation. It is contrary to the submitted evidence to suggest, as stated by the Sponsor, that the drug particle size is between 1 um and 10 um. **It is apparent from the submitted specifications, that up to a quarter of the particles in the formulation samples studied could be larger than 10 um, with an unknown number of the particles smaller smaller than 1 um.**

Safety relevance of liposome size

Consequently, it must be concluded that even the most essential parameters of the drug formulation were presented by the Sponsor in a manner contrary to the facts, or, at least, without all the facts being accounted for. In other words, even the first sentence in the section on the Drug Substance can, at least, be considered incomplete, or misleading under the most common rules of medical and scientific scrutiny. At the same time, it should be emphasized **that an accurate information on this point is considered essential** as we try to determine, and, perhaps, explain the safety of the drug in Phase 1 trial, and beyond.

Liposome nature of the drug

It is concluded that 1) The drug substance, most likely, is not a lipid encapsulated microbubble, meaning that it contains mostly a gas, and 2) it is not composed of particles only between 1 um and 10 um in size. Upon activation, it is, most likely, a **mixture of liposomes of variable sizes which undergo modification in size and other physical properties as the time interval from activation to injection increases.**

Drug's appearance and a lack of concern about liposome size early on

The physical properties of the drug substance and how they related to the drug use were described in Phase 1 protocol as follows (Vol.53, p.104, par. 4): *"Each dose of MRX-115 is offered in a 2 ml clear bottle with an airtight polypropylene seal and aluminum crimp. It is uniformly cloudy, colourless, sterile with a fill volume of 1.5 ml and a headspace of the active gas. The drug will be activated by on-site agitation (modified dental amalgamated shaker ...). After agitation, MRX-115 appears as a white, creamy foam, that will separate upon prolonged standing (1-2 hours). If separation occurs, simple hand agitation will redisperse the material into a homogenous solution. Drug should be used the same day as preparation within 8 hours."*

Liposome size and safety

Clearly, the concern about the liposome size or other physical properties was minimal at the time and agitation was recommended only if the separation occurred. Consequences of this concern, or lack of it, will become apparent later, when we will examine the safety of the drug in Phase 1, a dose-ranging study with normal volunteers.

Safety evaluation in Phase 1

Phase 1 trial (DMP 115 – 900) was meant to be a single center, single blind, placebo controlled study with a 7 day and 21 day follow-up period. On day 7, BUN and creatinine was measured, as well as a semi-recumbent blood pressure and heart rate. On day 21, clinical laboratory test were done, measurements of blood pressure and heart rate and the subject was discharged from the study.

Limited attention to ADEs

There was no reference to ADEs in the plan for the subject follow-up beyond day 1.

Absence of description of placebo formulation

The follow-up period was mentioned in the design of the study, but what the placebo should be was never defined in the protocol. The drug, with the physical properties as described above under Drug Substance, was administered as an intravenous bolus injection at five different doses 0.005 ml/kg, 0.01ml/kg, 0.02 ml/kg, 0.050 ml/kg and 0.1ml/kg to 4 normal males per each dose. The presumed placebo (glycerin, polypropylene glycol and NaCl) was to be administered to 10 additional subjects.

Results of Phase 1 and Phase 2 studies

The results of vital signs evaluation in this and a similar Phase 2 study, as presented by the Sponsor, are attached to this review as Appendix F, a. Likewise, the results of ADE reporting of the same subject population is attached as the first page of Appendix H.

It is apparent at first glance that a clinically significant change of more than 20% in vital signs occurred in large percentage of normals receiving the drug. There is only a small difference when compared to placebo. Although a drug effect may be expected, **the large placebo effect occurring in a large percentage of normal young men is a reason for concern.** (Not only a large percentage of normals was involved, but the changes were 40%, 60%, 80%, even over 100%)

Lack of concordance between ADEs and clinically significant changes in vital signs

The second main finding is the discrepancy between the low reported rate of ADEs in the subjects receiving placebo and the actually measured clinically significant changes in vital signs. Namely, the entire list of ADEs consisted of a case of influenza-like symptoms, a case of diarrhea and two cases of headache. This could hardly be truly seen in the same healthy subjects who exhibited more than 20% change in resting DBP in 11 out of 16 instances, for pulse rate in 9 out of 16, for respiratory rate in 10 out of 16 and for SBP in 4 out of 16.

This is interpreted as possible underreporting of ADEs.

Early safety warning signs yield no adjustment of future clinical protocols

This conclusion should have lead to a repeat of the first clinical study, but the Sponsor apparently dismissed the warnings from the first clinical study and immediately pursued the drug development in patients.

Drug safety profiles in normal volunteers and patients appear similar

The clinical studies in patients revealed largely similar patterns as those seen in Phase 1 and Phase 2 studies with normal young male volunteers. The underreporting of ADEs, although it cannot be documented, should be suspected in pivotal trials. The

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quantitative measurements, be it vital signs, electrocardiography, clinical chemistry or hematology, once again, speak for themselves as discussed below.

Second type of inappropriate estimation of ADEs

The sponsor introduced a serious bias into the safety drug evaluation in ISS by reporting only selected categories of signs and symptoms in the main tables on ADEs (showing only those with 1% or more normals or patients) and results of the laboratory measurements (only those with 15% or more patients with abnormal results). The errors like these could have lead the Sponsor to serious misunderstandings about the true safety of the drug.

Safety Update

The submitted Safety Update dealt with 61 patients dispersed into 5 trials as apparent from **Submission 4/7/99**, Table 1.1, p. 005. Four of these five trials were Phase 2 events and only one patient was from a Phase 2/3 trial. These patients received bolus injection, infusion, or both and the doses were different for each of the trials. Because of this variability it is baseless to attempt to group them and a separate evaluation is not warranted. In addition, from the safety parameters the Sponsor reported only the new onset adverse events.

ADEs in bolus injection

With the dose 20 – 50 ul/kg by bolus injection, out of six subjects, two were reported with pain, otherwise nonspecified, and of unspecified duration which resolved with medication the same or next day, and one subject was reported to have a headache and chest pain, also of unspecified duration, both characterized as mild (p.000024).

ADEs during continuous infusion

With infusion 40 ul/kg, Trial 011, four out of 12 patients had episodes of chest pain or shortness of breath which may be temporally linked to the time of infusion. One of the patients also experienced dizziness. Some of the time effect relationships cannot be shown because of lack of data provided.

In the infusion trial with 1.3 ml or 2.6 ml in 50 ml saline out of 32 patients, three had either tongue pain, hives or headache. A temporal relationship may exist between the drug infusion and the onset of ADEs.

The remaining trials with 10 and 1 patients, respectively, did not report any adverse events.

Conclusions from the safety update

It seems clear, from the Safety Update, that even with infusion of the drug, ADEs occur and not enough data exists to establish, or exclude temporal, or other relationships. Likewise, although some data was presented, it is not by far clear what is the optimal time from activation, agitation, or re-agitation to injection of the drug. Knowing only in few instances the time of activation and the time of injection, or infusion, is by far not sufficient to establish any clinically meaningful relationship.

Submitted erratum

As a part of the Safety Update of 4/7/99, the Sponsor submitted an Erratum which comprised about a half of that submission. It dealt with minor changes in vital signs in normal volunteers and the overall impact of these changes can be seen by comparing the original Table 35 in ISS (Vol. 49, p.140) with that submitted as a part of the Safety Update, p.000255 (Copies of both tables are attached to this review as Appendix F). The changes in DBP, pulse rate and respiratory rate do not change my initial assessment of the safety profile which will be commented upon later. Some of these new values (for example, DBP) were actually incorporated into my discussion of placebo controlled safety trials.

10.1 Deaths

The Sponsor reported 5 patient deaths in this NDA submission and the narrative summaries were provided (attached to this review as a part of Appendix A).

In all of these instances the patient started to experience significant cardio-pulmonary events such as atrial fibrillation and flutter, life-threatening bradycardia, pulmonary embolus, or had cardiac operation within day(s) of the drug injection (PCTA on the day of dosing, CABG next day and death in 14 days). Most of these patients were older subjects with a history of cardiac or liver pathology.

It would be difficult to trace these events to the drug injection from the data made available by the Sponsor. However, a relationship cannot be excluded if it could be demonstrated that the drug product remains in the body for an extensive period of time. Although, it seems, that the Sponsor studied the pharmacokinetics of the active substance, perfluoropropane, clinically, the fate of the liposome vehicle is less clear. Likewise, the potential contribution of sturdy liposomes to the generation of cardiopulmonary events related to pulmonary embolism is not known, but it cannot be excluded. The potential role of the liposomes of particulate nature in the generation of cardiopulmonary events was discussed earlier in this review.

10.2 Discontinuations

The sponsor reported a total of 10 discontinuations. Two occurred in the initial pivotal cardiac study, one in the second cardiac study, six were reported in the pivotal radiologic study and one in the pharmacokinetic trial in patients. The Sponsor's description of discontinuations is attached to this review as a part of Appendix A. All these patients were discontinued after first injection and none received the second injection.

Except for one patient, in whom the apparent reason for discontinuation was a hypersensitivity reaction with urticaria and pruritus (DMP 115 – 005, Patient 15/Site 4), all other patients experienced dizziness, chest pain, dyspnea or back pain at one time or another. The immediate causes of discontinuation were not given. These patients tended to be of middle age with only 2 of them 52 years and older (58 and 62 years of age). One half of these patients received 30 ul/kg DMP 115.

Adverse events appeared within minutes (1 – 15 min) of the drug administration, were of moderate intensity and resolved usually without treatment within minutes or hours of onset. In one instance the patient was treated with oxygen for 2.5 hours. The latter patient (DMP 115-010, Patient 106/Site 13) had been given a single dose 30 ul/kg DMP as a bolus injection. Approximately 4 minutes after dose administration, the patient began to have abdominal pain, back pain and cramping, all of severe intensity. Another patient which was treated with oxygen (DMP 115 – 009, Patient 207/Site 2) had also received 30 ul/kg and within 1 minute began to have headache, chest pain, nausea, flushing, paresthesia toothache and taste perversion. All AEs resolved within 1.3 hours with oxygen via nasal canula and acetaminophen. The latter was a 38-year old woman.

The most remarkable demographic factor of these patients with the discontinuation was a relatively younger age (41.5 years vs 55.4 years). Although some of these patients had a significant pathology, in most instances it was not immediately life-threatening (unstable patients were excluded). The fact that these patients had to be discontinued points toward a **potential risk for the use of this drug in a broader sense. That is, in patient populations other than those composed of elderly, or those with an apparent cardiac impairment.**

10.3 Significant/Potentially Significant Events

The average age of the patients with serious adverse drug events was 61 years. Of the 11 patients, four were from the first pivotal cardiac study, five from the radiological pivotal study and one each from two nonpivotal studies.

In this group, the adverse event is reported to occur usually within days of the drug injection (2 –15 days). The patients from the radiologic study usually received both drug

doses (10 ul/kg and 30 ul/kg) while those in the other two studies received one dose, 10 ul/kg.

In about half of these cases the adverse event appeared to be an exacerbation (in a patient with a history of MI, or congestive heart failure, atrial fibrillation, diabetes) or a new onset of cardiovascular symptoms (patient hospitalized 3 days after dosing for cardiac cathetrization with a bypass surgery later, or a patient with wound dehiscence), while in the rest a coincidence could have played a role (surgical removal of squamous cell carcinoma, total left nephrectomy for renal cell carcinoma, cholecystectomy).

10.4 Other Events

It is noted that out of 126 patients who participated in DMP 115 – 006 and – 007 only one of the cases was discontinued. In other pivotal trials a significant proportion of patients were discontinued, had a serious ADE, or died. It was 10 out of 211 patients for the cardiac studies (DMP 115 – 004 and – 005), and 13 out of 209 (DMP 115 – 009 and – 010). These numbers indicate an unexplained difference in (DMP 115 – 006 and – 007).

10.5.1 ADR Incidence Tables for Pivotal Trials

Use of an inappropriate placebo

The Sponsor performed an apparent placebo-controlled trial with **normal volunteers** in whom safety was monitored on several occasions (Trials DMP 115 - 900, - 901, - 905). The placebo in these instances presumably consisted of glycerin, propylene glycol and sodium chloride. No justification for the use of this placebo formula was presented in this submission.

No reason to dismiss observed safety data

There is no medical or scientific reason, to dismiss the AE incidence in **normal volunteers** as inconsequential (Vol. 49, p.66, Table 8). The main concern is whether glycerin and particularly propylene glycol cause a headache, diarrhea or influenza-like symptoms. If so, then the incidence of AEs due to the drug is not similar since it has no true placebo counterpart. Consequently, the number of AEs found, 22.9% could represent the true occurrence of "AEs occurring in $\geq 1\%$ of healthy volunteers." (In addition, it is methodologically unacceptable that the Sponsor limited the analysis only to those AEs, which have equal or greater incidence than 1%).

Underestimation of observed patient safety data

Regarding **patients**, the Sponsor inappropriately chose to disregard headache as the most frequently reported AE occurring in $\geq 1\%$ subjects because the findings for the drug and placebo were similar, for the reasons mentioned in the introduction to this section. The overall incidence of AEs in patients was 25.2% including 16.2% which were mild, 5.7% moderate and 3.3% which were serious. (Vol.49, p.68, Table 9, P.68). The medical context of occurrence of a headache could be quite different (for example, related to concomitant localized CNS effects of the drug) than that which the Sponsor implies, namely, an inconsequential episode (for example, related to concomitant cardiovascular effects of the drug). As mentioned earlier, the placebo patients may not be representative of the entire sample. In addition, the Sponsor unjustifiably pooled the back pain and renal pain AE data. This may obfuscate an appropriate evaluation of the drug's renal effects.

Use of different categories to report ADEs in normal volunteers versus patients

It is also noted that the Sponsor chose to present different patient categories in the tables on AEs for normal volunteers and patients in Integrated Summary of Safety (Vol. 49, p.66 and p.71, Table 8 and Table 10). To reiterate, the value of presumed placebo comparisons is limited as only about 1/4 the subjects took placebo.

Difference in deaths and ADEs between drug and "placebo".

The most important conclusion from the Integrated Summary of Safety in the so-called placebo-controlled study (Vol. 49, p.66 and p.71, Table 8 and Table 10) is two deaths. None of the patients who received placebo (saline) died. Almost as importantly, but not unexpectedly, the drug was associated with AEs related to cardiovascular system including chest pain in 11% patients, with no comparable effect in any of the patients receiving placebo. Although the relevance of the placebo is doubtful, it may still be worthwhile to note that the overall incidence of AEs in patients was about 35% (Vol. 49, p.71, Table 10, also in Appendix H to this review).

Unexpected, unusual dose-response relationship between drug dose and ADEs

Categorization of AEs by the dose administered showed characteristic trends (Appendix H). With $< 10 \text{ ul/kg}$ DEFINITY, there is a relatively greater incidence of **headache and chest pain** 20% (3/15) and 13.3% (2/15), respectively, while, with 0 % (0/15) for back pain/renal pain, 0% (0/15) for abdominal pain, 0% (0/15) for dyspnea and 0% (0/15) for flushing. On the other hand, with $> 20 \text{ ul/kg}$, the higher dose, statistically significant increases were seen for **back pain/renal pain, abdominal pain, dyspnea and flushing** showing 5.4% (13/242), 4.1% (10/242), 2.5% (6/242) and 5.4% (13/242), respectively (Vol. 49, p.75, Table 11), while only 3.3% (8/242) for chest pain and 5.4 % (13/242) for headache. This roughly approximates the distribution one would expect from the effect due to particle size. Consequently, it is doubtful whether

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decreasing the dose, or the drug administration by infusion is advantageous, or even safe.

With the **small** dose (<10 ul/kg) there were also 3/15 (20%) of patients who had a **fever**, an additional case of upper respiratory infection, a case of arrhythmia and a case of thrombosis of retinal artery, although for the latter, according to Sponsor, "*The investigator concluded that this finding was probably present prior to DMP dosing*". Overall, the incidence of AEs with the smaller dose was a surprising 60%(9/15), and only about 30%(84/242) with the higher dose.

Variable occurrence of ADEs in different trials

Those conclusions are supported by the Sponsor's statement "*Of the AEs of interest only back/renal pain, chest pain and headache occurred in >- 1% of the patients who received an infusion.*" (Vol. 49, p.79, l.1). However, the rate of AEs seems to vary widely depending on the number of factors among which according to the Sponsor is, for example, indication. **the overall rate of reported AEs was only 10% (as opposed to 60% in cardiology trials, as mentioned above) with the small dose and was also relatively lower with an extreme dose 30 ul/kg (18%). The overall rate of AEs also varies, according to the Sponsor, depending whether the drug was sterilized or not. The overall AE rate was 50% higher in patients receiving the sterilized product (Table 16, Vol.49, p.90) than in patients with sterilized product. It is, however, uncertain whether the sterilized product was not already sterile without the sterilization. It is possible, that the sterilization alters the drug product in some other way so as to have an effect on AEs.**

Patients with COPD

The sponsor also specifically evaluated the overall rate of AEs in two patient sub-populations. A direct comparison between healthy volunteers and patients with COPD showed 58.3% in the latter group and only 33.3% in their healthy counterparts (Vol.49, Table 21, p.106). The severity of COPD was not described. However, there was almost no difference when the same comparison (non-COPD vs COPD; 24.5% vs 23.8%; Table 20) was done in patients with heart disease. Likewise, the patients, with and without CHF among the cardiac patients had a similar overall rate of AEs (28.4% vs 22.9%) (Table 19; Vol.49, p.101).

Conclusions on ADEs in patients

Overall, the rate of AEs in patients varied widely from 10% to 60%. The **largest relative number** was observed with 15 patients who received the **smallest dose** by bolus injection. Also, the patients with COPD exhibited a large rate of AEs (58.3%), but only when compared with normal volunteers, where it was only about 25%. In addition,

the large fluctuations in AEs rate such that seen, for example, among patients receiving the smallest dose by bolus (60% vs 10%), or the reversed trends among the groups of patients (cardiac vs other patients) in reference to the dose (60: 10 vs 10: 30) are largely inexplicable by any of the Sponsor's argument. Moreover, it is of concern to this reviewer that those obvious discrepancies have not been addressed in the NDA submission.

10.5.2 Laboratory Findings, Vital Signs

Laboratory Findings

Abnormal shifts considered only when affecting 15% normal volunteers or more

The Sponsor took an unusual approach to the analysis of laboratory and chemistry data. As it can be seen from the ISS in the original submission (Vol. 49 -54) as well as from the Safety Update (Table 23, p. 000234 and p. Table 25, 000237), there were statistically significant changes due to the drug in numerous hematology and chemistry parameters for **normal volunteers**. This was highly unusual. Regardless, the Sponsor presented next the **tables showing abnormal shifts for each of the parameters, but only those which affected 15% or more normals** (Table 24, 000236 and Tables 26 and 27, 000238). The Sponsor cannot accurately assess the safety of the drug without first assembling the available data in a way conducive to such an analysis (The respective tables and the accompanying narrative by the Sponsor are attached to this review as Appendix E).

Abnormal hematology and clinical chemistry findings in normal volunteers

The Sponsor reports that due to the drug a decrease in hematocrit (from normal to low) occurred in 15.9% **normal volunteers** (38 men and 6 women, average age 31.8 years, Table 24). In addition, for example, chloride decreased (normal to low) in 25 % normals on placebo and 18.2% on DMP 115 (Table 27). Those findings are also highly unusual given the subject population. The drug also decreased TT (thrombin time) and aPTT (activated partial thromboplastin time) in **normal subjects** on DMP as well as TT on 'placebo' in 31.3%, 25% and 37.5% subjects, respectively. Although this finding is of no immediate clinical importance it points out towards a profound alteration, most likely of the liver function, which is also suggested by other data from these tables.

Patient safety data analyzed in an unacceptable way

The **patient data is analyzed in a similar unacceptable way**, including the listing of the shifts in 15% or more patients **only** for clinical chemistry (Safety Update, Table 31, p. 000249 and Table 34, p. 000253). Apparently, for the same reason, no table of shifts whatsoever is presented for hematology laboratory evaluation.

Abnormal hematology and clinical chemistry parameters in patients

In addition, a brief look at the clinical chemistry data in the Integrated Summary of Safety (Vol. 49, p.131 – 133) reveals a peculiar pattern of findings. Statistically significant changes occurred in albumin, total protein, alkaline phosphatase and lactic dehydrogenase. This would suggest a potential drug effect on liver function. There could also be a potential effect, although to a lesser degree, on calcium, chloride, BUN, creatinine and CO₂. These changes occurred as early as 40 min after the first injection, but there was no data on potential earlier changes which could be of essence in the assessment of the drug effect on electrolytes and inorganic ions (Mg, Ca and P).

The effect of the drug on the kidney is suggested by the changes in BUN, creatinine, potassium and chloride, while the effect on the liver may be indicated by the changes in albumin, total protein, alkaline phosphatase and lactic dehydrogenase. An early effect on CO₂, which may be present, could also point toward the lungs as a potential site of the drug action.

Although a change in glucose is also reported, such a result may be caused by diet and should not be overemphasized, as non-fasting blood samples were drawn.

There appears to be a minor effect of the drug in patients on the most of the hematology parameters except for basophilic and platelets, which would not be unexpected when the drug is injected as a particulate. Particles of small diameter are known to be trapped in the bone marrow and may affect hematopoiesis, release of the blood cells from the marrow and change in lymphokines.

Vital Signs

Data analysis is inappropriate

The safety data in the section on vital signs in the Integrated Summary of Safety (Vol.49, p.139 - 146) is probably not accurate. First of all, in regard to patient data, the table on Absolute Change From Baseline in Vital signs Measurements (p.146) totally disregarded any relationship to the time of the drug injection which is crucial.

More importantly, in the only other table presentation of patient vital signs (Vol.49, p.143), without an explanation, a comparison is made between a would-be baseline and subsequent measurements. **The time points after the baseline, however, do not refer to the time of the exposure to the drug, but to the time after the completion of echographic imaging session.** Therefore, the line "2 min post-1" does not really mean 2 min post-injection as it would be reasonably implied, but it indicates the time period starting at least 7 min postinjection because the imaging session itself lasted at least 5 minutes.

Finally, the argument, which is made regarding a comparison with placebo, is moot. How can only 42 cardiac patients from multiple medical centers be representative of 566 cardiac and other patients, particularly those in the group of patients with liver and kidney disease? Can such a comparison, when made, be reasonably valid one?

Safety data collected close to the drug injection was not obtained

This issue was brought up and corrected (p.18, next to the last paragraph), in this review, already in the section on safety of the respective protocol as follows: "vital signs - pre-injection, 7 min, 15 min, 20 min, 35 min after each of two injection and then approximately 24 hr, 48 hr and 72 hr post-injection (Vol. 62, p.55, par 2, l.1 and Protocol, Vol. 62, p. 217, par.2, l.1)". Therefore, there is, in fact, according to the Sponsor's presentation, no complete data on vital signs in respective trials within 7 minutes post-injection.

The table on Mean Change From Baseline in Vital Signs (Vol.49, p.143) shows only statistically significant decreases in pulse rate, systolic and diastolic blood pressure within about 30 min of the drug injection. In reference to pulse rate this decrease appears to deepen with the second drug injection.

Clinically significant data and other related data missing

The earlier mentioned table on Absolute Percent Change, documents a change (likely mostly a decrease) in DBP in the category >20% to 40% in 31.1% patients (176/566); >40% to 60% in 4.2% patients (24/566); >60% to 80% in 1.6 % patients (9/566) and there were 2 patients with a greater than 80% change. Even with this unfavorable picture the Sponsor concluded: "*In-summary, this patient population with many illnesses, there were no clinically significant changes in SBP, or DBP pulse rate or respiratory rate due to DMP 115 dosing*" (Vol. 49, p.146, p.1, l.1). **It should be pointed out that the earliest ECG data for the population of patients included in both tables on vital signs in patients in the Integrated Summary of Safety (DMP 115-004 and -005) was obtained not sooner than about 1 hour, or more post-injection, as it will be discussed in the next section. A more detailed analysis of the Absolute Percent Change was done by this reviewer for the large segment of the studied population in which DBP changed >20% in pivotal studies (Table 1, page 23 of this review, and related database).**

Persistence of clinically significant changes and lack of follow-up

The percentage of patients who had this change (20% or more in DBP in the cardiac anatomy studies with 5 ul/kg was about 15% at 7 min post-injection. In one trial (DMP 115 - 005) this proportion remained about the same for the entire time period

measured, that is 72 hrs. In the second trial it fluctuated from 8.8% to 29.4% at 22 min after the second injection, but **at 72 hrs it was still 14.7%** (DMP 115 - 004). Please, refer also to page 21 of this review for more details.

For the patients who received 10ul/kg, this percentage was 2% after 7 min and tended to increase, being 10.2% after 72 hrs in one trial (DMP - 005). In the second trial (DMP - 004), it was 11.8 % at 7 minutes and later more or less steadily **increased to surprising 41.1% after 72 hours.**

In the second study (DMP 115 - 006 and – 007) these percentages were about 10% at 8 min post-injection, varied slightly and remained at about **10% patients at 24 hrs.**

10.5.3 Special Studies

10.5.3.1 Electrocardiography

Lack of data temporally related to drug injection

The limitations, stated in the introduction to this section on safety, fully apply to the electrocardiographic exams. In addition, the Sponsor asserts : "*Because measurements were not taken at the same time points in all three trials - pivotal trials, data have been pooled and presented as the maximum absolute percent change from baseline.*" (Vol.49, p.147, par. 3 and Vol.49, p.152, par. 2). This was applied to both the normal volunteers and all the patients. Therefore, the findings were generally treated by the Sponsor the same regardless whether they were obtained 1 hr or 72 hr following the procedure. It should be emphasized, once again, that **no adequate evaluation was done in respect to ECG during the most relevant period, up to 60 min post-injection.**

Placebo dilemma

As reasoned before, a comparison with placebo should be considered noncontributory for the normal volunteer group. Likewise, among the patients there is no apparent reason for evaluation of the subjects within the placebo group (the number of patients is small and, therefore, it cannot be representative of the rest of the population studied with the drug) in the larger context (for a comparison with the drug effect). In addition, the investigator, or technician in charge always knew in advance whether a particular patient had received placebo, or the drug.

Inappropriate interpretation of QTc and other data

Even if the patients with a pacemaker are excluded, there are still 2 patients (10%) which became a risk for the deadly arrhythmia due to the exposure to DEFINITY. The potential effect of the drug on patients wearing a pacemaker may be too complex to explain point by point. However, it is not difficult to figure out that a myocardium made, even temporarily, ischemic by the drug could potentially fail when paced without an adjustment for the ischemia.

QTc changes in patients other than those with predominantly cardiac disease

As mentioned before, it could be helpful to assess the cardiovascular effects of the drug in some population other than that with a known, or suspected cardiac disease.

Unfortunately, these safety evaluations are incomplete as only two ECGs were done on these patients, one pre-injection and the second only 24 hrs after the second DEFINITY injection. That is unacceptably late. In addition, the patients in these trials received a double dose of the drug. **The results in regard to QTc change seem still disturbing.** In trial DMP 115 - 009 (Vol. 224, pp. 207-219) the occurrence of prolongation of QTc interval of concern was about in 5% patients. In trial DMP 115-010 (Vol. 228, pp. 199 - 211), about 8% of patients had an average increase 39 msec with the largest increase 57 msec.

Possible misinterpretation of QTc changes due to entering wrong primary data

However, the Sponsor dismissed all these ECG questions, due to the trial design and execution, or actual values, as unimportant and concluded that no ECG findings were considered clinically significant. The sponsor also did not provide in the original NDA submission the line listings for corrected QT intervals, substituting uncorrected values in numerous instances (Vol. 207 and Vol. 211). Therefore, there is a concern whether the corrected QT interval and QTc interval change values were actually incorporated into the respective summary tables provided by the Sponsor, as referred to earlier in this section.

10.5.3.2 Neurological Evaluation

Apparent absence of neurological effects of the drug

The Sponsor described the results of a basic neurological evaluation in 42 normal volunteers and 56 patients and asserts that there was no effect of the drug in these subjects.

In 12 healthy volunteers and 447 patients a mini-mental state examination was performed. An obvious decrease in some of the parameters was described only in one of the healthy volunteers.

Lack of concurrence of quantitative and qualitative findings

None of the parameters tested, however, was quantitative. Thus, although the results of the studied indicators do not appear alarming, this is in a sharp contrast with all the quantitative safety parameters. It is unlikely that a drug affecting vital signs, ECG, clinical chemistry and hematology, that is all the quantitative parameters measured, to such a degree as shown here for DEFINITY, would leave the nervous system spared. **Rather, it is conceivable, that the nonquantitative safety parameters were underestimated here.** This may hold not only for the neurological assessment, but could equally apply for the ADE observations and their recording.

10.5.3.2 Pulseoximetry

Limited extent of the study

Oxygen saturation measurements were performed in one pivotal trial (DMP 115 - 006 and - 007) and one other Phase 3 trial (DMP 115 - 0017). In the pivotal study the drug was administered as bolus while in the other trial it was used as both bolus and infusion.

Limits of usefulness when not measured in a timely fashion

The reason for the use of this methodology was not clarified, but presumably it would assess the effect of the drug as a particulate. Presumably, if the particles comprising the activated drug formulation would act as emboli in the lung, oxygen availability would decrease and so the oxygen saturation of hemoglobin.

However, oxygen saturation is clearly a multivariate phenomenon and the simple relationship as suggested holds, most likely, only for a short period of time after an embolic event, or other blood flow related disturbance, presuming, of course, that it is not a colossal, fatal event. Thereafter a multiplicity of compensatory homeostatic mechanisms kick in resulting in a skewed response of variable duration. Even without these compensatory effects, **a change of 6% or 7% in oxygen saturation could be an equivalent of one entire lung segment embolized, as transpires from a simple calculation.** This, in turn, is diagnostic of pulmonary embolism, according to the current practice.

Limits of information in available data

Consequently, the data on pulseoximetry, as provided by the Sponsor should be interpreted with utmost caution, as they were not obtained in a timely fashion. The most needed measurements, from 3 minutes before to 3 minutes after the drug injection, were not collected. The rest of the data on pulseoximetry, in the absence of the anchor values should only be considered an accessory information.

Preliminary pulseoximetry data are disturbing

In spite of the key data missing, it is hard not to see the few instances where there was as change up to 7 %, shifting the value from normal to the abnormal low range, and which remained such even at 24 hrs. This was an indicative of a potential drug effect, which even all the compensatory mechanisms in place could not handle. Thus, although no firm conclusions can be made from the pulse oximetry results provided by the Sponsor, because of lack of key primary data, the secondary pulseoximetry results do not look favorable.

10.5.4 Drug-Demographic Interactions

No drug demographic interactions were observed and recorded.

10.5.6 Drug-Disease Interactions

No drug-disease interactions emerged so far.

10.5.7 Risk - Benefit Evaluation

This NDA application inadequately investigated and/or described the drug substance, its safety and efficacy.

Excessive variability in safety data

In view of the great variability in the safety profile of patients imaged and cared for by different investigators as well as among individual patients it is suggested that a factor, or factors with a significant impact on the drug safety remained unaccounted for during this drug development. The data available so far seem to suggest that, at least, some of that variability is likely due to the drug substance itself, or its (un)intentionally modified forms.

While the pivotal studies used bolus injection, the intent is to administer the drug, manufactured differently, also by a continuous infusion

The review process revealed inconsistencies in preclinical toxicities between the original IMRx product and that manufactured by DuPont. This discrepancy was exemplified when one of the earlier IMRx experiments had been repeated with the DuPont product and unexpected animal deaths resulted, albeit with a somewhat larger than the originally recommended clinical dose. However, it should be noted that although earlier trials were done with a bolus injection, the current drug labeling calls for a continuous infusion. Therefore, in view of the unsuccessful preclinical trials, a substantial uncertainty about the dose remains.

Discrepancy between instructions to investigators and suggested optimal use

In addition, as noted earlier in this review, the Sponsor explained the discrepant results mentioned above by a potential effect of the time interval from drug "activation" to its injection, suggesting that this time period longer than 30 min is better from the safety standpoint. Yet, the protocols for the pivotal trials guide an investigator to inject the drug no later than 5 min after activation, or re-agitation. Thus, the drug might have been injected during the clinical trials when it is not as safe as it could be.

Lack of data on the time interval between activation and injection in clinical trials

The potential effect of the time interval from the drug formulation (activation, agitation, re-agitation) to its intravenous injection lead this reviewer into an evaluation of the drug substance with a special reference to this aspect. As stated earlier in this review, numerous insufficiencies can be found in the section on Drug Substance of this NDA submission.

Drug's physical properties may be responsible for the unfavorable clinical safety profile

The substantial lack of data in that regard, coupled with the total lack of clinical data on the length of time expired between the drug bolus injection and its activation, agitation, or re-agitation on Case Report Forms, combine into a large information gap. This can hardly be overcome at this time given the unfavorable clinical safety profile.

Unfavorable clinical safety profile seen despite the absence of the critical measurements around the time of injection

It is of essence to point out at this time, that the unfavorable clinical safety profile of the drug is revealed clearly despite the lack of data, once again, during the most important period for the safety assessment. This most critical span is during and within minutes after the drug injection as the drug is composed of liposomes. It cannot be overlooked that the Sponsor did not reliably measure ECG any earlier than 1 hr after the drug injection despite clear warnings that the drug obviously affected vital signs in Phase 1 clinical trial, that is in normal young males. Inconsistencies, obvious or less apparent, were discussed in this review also in monitoring vital signs and ADEs. It is suspected that had the vital signs and ECG been taken at appropriate times, the vital sign and ECG abnormalities would have been even more striking.

Abnormal safety profile in normal volunteers confirmed in trials with patients

The abnormal safety profile, seen especially in vital signs in normal volunteers, was confirmed particularly for vital signs, ECG and laboratory chemistry (Tables 3 and 4, pages 91 and 92 of this review) also in patients in pivotal trials. The data also showed a large variation in the two groups of safety parameters, vital signs and ECG, when sub-analyzed according to different investigators (Tables 1 and 2, pages 23 and 39 of this review). Although there might be alternative explanations, one of the reasons could be that different investigators injected the drug at a different time after activation. The idea should be entertained particularly in the absence of any Case Report Form data to the contrary.

Significant safety information gap persists

At the same time, at the time when this factor may be reasonably suspected as a significant safety factor, which is unaccounted for and not controlled, even statistically, throughout the entire clinical development of this drug, it would be unwise to affirm anything substantive about the drug overall safety profile.

Clinical significance of available safety data

The data collected during this drug development and described in this application could reasonably be interpreted as suggestive of significant hazard for a cardiac event, stroke and life threatening arrhythmias (TdP). Until these concerns will have been addressed and resolved this application will need to be deemed nonapprovable solely on the safety grounds, regardless how beneficial the drug may be regarded for clinical sonography.

Nature of efficacy data

Irrespective of its potential safety hazard, this drug may have only a modest benefit for the echocardiography. This benefit has been marginally documented in this NDA application, as the evidence to support it is mostly testimonial, circumstantial and subjective. Objective quantitative evidence is largely missing from this submission.

Sufficient evidence to demonstrate the endocardial border delineation

The only efficacy parameter which appears to be adequately described and discussed is the endocardial border delineation. However, even here the differentiation is between the evaluable as a positive finding, and the non-evaluable as a negative finding.

11. Conclusions

DMP 115 is the first intravenous liposome ultrasound contrast agent being considered for approval. Both intravenous agents approved so far, Albunex and Optison, were microspheres based on modified albumin.

DMP 115 contains perfluoropropane and phospholipids. The phospholipids are immiscible in water, and since saline is the excipient in which the drug is formulated, an inherently unstable system is formed during the drug formulation. When **the immiscible mixture is converted into an emulsion**, by a physical force, shaking, in this application referred to as "activation", liposomes of variable diameter (size) form. These are, likewise, unstable, as their characteristics, for example, concentration and size change substantially with time. To prevent an effect on efficacy, it is necessary, according to protocol, to agitate the emulsion by inverting the "activated" vial, and/or re-agitate. The changes in liposome size and concentration were mentioned, to some extent, in the NDA submission. **The scope of these changes, however, may be such that much more data is needed to characterize them fully.**

In addition, during the drug development, the manufacture of the drug formulation changed at least once, yielding, not surprisingly, at least, one significant change, a significant increase in concentration of liposomes.

The liposomes, due to their size and other physical and chemical properties, when injected intravenously, may potentially obstruct the blood flow and/or exert other

biological activity impacting on safety. Of a lesser concern is the gas component, perfluoropropane, which was described as an inert gas. However, the fate and transformation of liposomes (size, concentration, etc.) *in vivo* was not studied in this NDA application. In addition, the liposomes were investigated outside of the context of perfluoropropane only scarcely. This may confound the results, as the **statements made regarding perfluoropropane cannot be overinterpreted to mean the total drug formulation and, specifically, the liposomes.**

The safety and efficacy of this new liposomal formulation was investigated and the results were described in this NDA application.

It should be noted that particles of different sizes may have propensity for different organ and tissues, partly due to their size. This is well recognized and the concept has been used with advantage in imaging various organs. For example, while macroaggregated albumin (on average 5 – 100 μm in diameter) is used in diagnostic imaging of pulmonary embolism, the gold colloid (0.02 – 0.04 μm in diameter) used to be applied earlier in lymphnode imaging. As the DMP 115 formulation was described by the Sponsor to contain liposomes ranging in size from non-measurable to 32 μm in diameter, involvement in a variety of organs might be observed. On the other hand, if the drug did not affect safety in this manner the effects would be absent, or localized.

The **preclinical** studies showed (as per the Pharm/Tox review, Adebayo Laniyonu, Ph.D.) that the doses somewhat higher than those planned for clinical use yielded mainly pulmonary, hepatic and immunogenic toxicity. All three of these effects are compatible with the above hypothesis, although this may be somewhat indirect in regard to the immunogenic effect. The reason is that phospholipids in the drug formulation, are endogenous and, therefore, nonimmunogenic as such. However, **although those may not be immunogenic when present in low concentration as solutes, they may potentially become immunogenic due to their structural changes when presented to lymphocytes as liposomes, i.e. injected as liposomes.**

It is of **clinical** interest that the clinically significant pulmonary, hepatic and immunogenic changes were seen in the larger Phase 1 human trial (DMP 115 – 900) with normal volunteers (Table 3, next page). The pulmonary effect likely manifested in embolic event(s) and associated respiratory alkalosis, which resulted in an elevated chloride (Normal to High) in 50% of subjects on placebo (glycerol, polypropylene glycol and saline) and 40% of subjects who received the drug. This high response rate was seen even 24 hrs after the drug (placebo) injection, but was compensated mostly within the next 20 days (measured only on Day 1 and Day 21). The effect of the drug was

most apparent in normals who received the lowest drug doses (5 ul/kg: 40%, 2/5, one subject Day 1 and Day 21; the other subject Day 1 only; and 10 ul/kg: 75%, 3/4, all subjects Day 1 only). The change in vital signs, for example, a more than 20% change in DBP in about 68% of normals receiving placebo and a similar proportion of normals receiving the drug, can also be, at least partially, attributable, to the pulmonary effect.

Table 3

**Category or Grade Change in Selected Laboratory Parameters
in Young Normal Volunteers
(by dose in DMP 115 - 900)
(Vol. 196, p.183 -201)**

Test Dose	AST	ALT	LDH	Total Bil.	HCO3	Cl	Mg	P	Ig G
Placebo	20% 2/10	0% 0/10	10% 1/10	30% 3/10	20% 2/10	50% 5/10	20% 2/10	30% 3/10	0% 0/10
5 ul/kg	40% 2/5	0% 0/5	0% 0/4	40% 2/5	0% 0/4	40% 2/5	0% 0/4	0% 0/4	0% 0/4
10 ul/kg	0% 0/4	25% 1/4	25% 1/4	0% 0/4	25% 1/4	75% 3/4	50% 2/4	0% 0/4	25% 1/4
20 ul/kg	0% 0/4	0% 0/4	25% 1/4	0% 0/4	25% 1/4	25% 1/4	50% 2/4	25% 1/4	25% 1/4
50 ul/kg	0% 0/4	0% 0/4	0% 0/4	25% 1/4	25% 1/4	25% 1/4	25% 1/4	0% 0/4	0% 0/4
100 ul/kg	25% 1/4	0% 0/4	25% 1/4	0% 0/4	75% 3/4	25% 1/4	50% 2/4	0% 0/4	25% 1/4
Total									
Drug	14% 3/21	5% 1/21	15% 3/20	14% 3/21	30% 6/20	38% 8/21	35% 7/20	5% 1/20	15% 3/20

The hepatic effect (N to H, or H to HH) in AST or ALT was seen in 20% of normals receiving placebo and 15% of subjects receiving drug. Analogous to the pulmonary effect, the hepatic action was also seen, more with the lower drug doses (5ul/kg and 10ul/kg). The immunogenic effect was observed as a systematic substantive (almost doubling in some instances) elevation in serum IgG in all subjects tested regardless whether they received drug or placebo (glycerol, propylene glycol and saline). Within these increases, there were changes from L to N categories in two out ten normals on placebo. In the subjects treated with DMP 115, a change from N to H was seen in one out of four subjects each for doses 10 ul/kg, 20 ul/kg and 100 ul/kg. Other clinically significant clinical chemistry changes which occurred in normals, both those on placebo as well as those receiving the drug, were increases in Mg (20% vs 35% respectively)

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS DPM 115 - DEFINITY and ESR (20% vs 25%), among other less pronounced, or less frequent abnormal parameters (for example, P was elevated in 30% (3/10) of normals who received placebo, but only in 5% (1/20) of those who received drug).

The pattern observed in preclinical trials and the clinical studies with normals was also demonstrated in pivotal studies **with patients**. The minor deviations from this pattern, which occurred, will be specifically mentioned.

Evidence of liver injury as suggested by increases in transaminase from a normal range in ALT and AST were recorded in both trials with the most complete safety data, DMP 115 - 004 and DMP 115 - 005 (Table 4, this page). They were observed in 10 % patients for ALT and 14% patients for AST in DMP 115 - 004. The respective percentages for DMP115 - 005 were 18% and 11 %. This roughly agrees with the combined total of 20% for normals on placebo, and 15% for normals who received drug. In about half of cases where this occurred, the increases were concomitant. In a number of instances these increases persisted beyond the 72 hr observation period.

Table 4

**Category or Grade Change in Selected Laboratory Parameters
in Response to DMP 115 in Patients**
(in DMP 115 - 004 and 005)
(Vol.207, pp.197-245 and Vol.211, pp. 100-170)

Test	AST	ALT	LDH	Ca	Creat	BUN	Na	K	Cl
DMP 115 - 004	17% 12/69	10% 7/69	9% 6/69	30% 21/69	11.5% 8/69	13% 9/69	7% 5/69	6% 4/69	16% 11/69
DMP 115 - 005	11% 11/100	18% 18/100	8% 8/100	25% 25/100	9% 9/100	8% 8/100	7% 7/100	5% 5/100	8% 8/100

For the reason which is not immediately apparent at this time, the increases in serum chloride which occurred so frequently in normals, with placebo as well as the drug, were not so evident (only 8% in DMP 115 - 005) in the patient population. One of the explanations could be that the compensatory mechanisms to the drug effect differ between young normal volunteers and older patients. This mechanism in patients could

involve calcium levels which fluctuated considerably after the drug in patients only. Fluctuations among categories (L,N,H) or among degrees of change (+, ++, -, --) in serum calcium, which were defined in advance, reached 30% in DMP 115 - 004 and 25% in DMP 115 - 005. Although the effect of placebo (saline) here was about 15% and 12.5%, respectively, the high remaining proportion of patient population exhibiting large swings in serum calcium was unexpected and unexplained.

The patient population showed a significant number of patients, about 10% in each of the key safety trials in which creatinine was elevated due to the drug. About one half of these patients had this elevation persisting beyond the 72 hrs measurement. These patients were not followed farther. A similar number (about 10%) showed an increase in BUN. This would suggest an effect of the drug formulation on kidney in patients, an action which may be long-lasting, similar to the effect in the liver.

About 5% - 7% patients also showed an elevation in sodium and potassium. Considering also the fluctuations in calcium in patients as well as increases in Mg and P in normal volunteers, the tendency of the drug to increase most of electrolytes and inorganic ions may indicate an impaired filtration by the kidney. Lodging and/or impaction in the renal circulation of liposomes, or their remnants is a plausible explanation.

With the preceding in mind as a background, **the finding of large effects of the drug on vital signs and ECG, as described in detail earlier in this review, appears consistent with all the other safety data.** The vital signs, particularly DBP changes after DMP 115, are quite similar in magnitude and frequency when normal volunteers (about 68% with a more than 20% change) and the patients are compared. Although for some investigators the frequency of the 20% change in DBP in patients is much lower than in others, for other investigators it agrees quite well with what is seen in normals, as apparent from Table 1 (page 23 of this review). The ECG data (Table 2, page 39 of this review), although the first was recorded about 1 hour after the first exposure to the drug, is similarly disturbing.

Also in this view, and as commented before, **reporting of relatively few ADEs of serious nature is inconsistent with the rest of safety data,** i.e. quantitative safety data. In addition, it is this reviewer's opinion that ADEs reported by the Sponsor as renal/back pain as well as the headache are likely obstructive in origin.

Regrettably, **the safety database submitted as a part of this application is not complete** as the data submitted does not substitute that which is missing. Pulseoximetry recorded starting 3 minutes after injection cannot replace the

measurement obtained starting at the time of injection. Similarly, vital signs obtained 3 minutes, or 7 minutes after the drug injection do not reflect events immediately after the drug injection. ECGs taken starting at about 1/2 hour, or an hour after the drug injection are not informative enough when there is reason to believe that there is a serious safety concern.

12. Recommendations

The application is not approvable at this time on safety grounds, as the available safety data **does not exclude** a significant hazard for myocardial event, stroke and a life threatening arrhythmia.

As all the reliable key safety parameters, primarily, vital signs, ECG and even pulseoximetry demonstrate grossly abnormal data in a large proportion of normal as well as patient population, even when always measured late, it is imperative to require more safety data prior to approval. The drug effect on vital signs, ECG and selected laboratory parameters largely **was not dose related** suggesting that even the lowest dose used was not safe.

Although the pivotal trials did not meet the regulatory criteria for two adequate and well controlled studies, as a **substantial bias was involved** in the performance of each, it appears that the claim for the Endocardial Border Delineation was, at least partially, substantiated.

The Sponsor should attempt to develop this agent starting with an unequivocal demonstration that the drug in the present, or a modified form, is devoid of embolic potential.

It is absolutely essential that the future data on pulseoximetry, vital signs and ECG is obtained in a **timely manner**.

Immunogenicity studies should be repeated with focus on measuring specific antibodies, not classes of antibodies.

The Sponsor should provide the summary safety tables which include **all** occurrences of clinically significant abnormalities, including vital signs, ECG and laboratory parameters; not only selected parameters and cases.

13. Labeling (Please refer to Draft US Package Insert, Vol.1, pp. 24 – 42)

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the approval package consisted of draft labeling

DRAFT LABELING

Medical Officer

TS

7/12/91

Appendix A

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Appendix A

APPENDIX D.2 - NARRATIVE SUMMARIES

- Appendix D.2.1. Narrative Summaries for Deaths**
- Appendix D.2.2. Narrative Summaries for Serious Adverse Experiences other than Deaths**
- Appendix D.2.3. Narrative Summaries for Safety-Related Discontinuations**

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APPENDIX D.2.1. - NARRATIVE SUMMARIES FOR DEATHS

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APPENDIX D.2.1 - NARRATIVE SUMMARIES FOR DEATHS

Study DMP 115-004

Patient 1/Site 9

This 33-year-old black male had a history of CHF (NYHA Class II) and idiopathic dilated cardiomyopathy. In 1988, he had a heart transplant, and 2 months prior to the start of the trial he experienced atrial fibrillation. On April 2, 1997, he received two 5 µL/kg doses of DMP 115, each given as a bolus. Ten days after DMP 115 administration (April 12, 1997), the patient went to the emergency room with epigastric pain (abdominal pain) and shortness of breath (dyspnea). He had atrial fibrillation and atrial arrhythmia (atrial fibrillation and atrial flutter) with a heart rate of 140 bpm, electrolyte imbalance, and questionable CHF. The patient was admitted to cardiothoracic surgery service. On April 14, 1997, the patient had ventricular fibrillation (ventricular fibrillation) and ventricular tachycardia (ventricular tachycardia). Following two attempts at cardioversion, the patient had electromechanical dissociation with idioventricular rhythm and cardiac arrest (cardiac arrest). The patient died on April 15, 1997. The investigator considered the death to be a consequence of chronic transplant rejection with progression of the disease state and unrelated to DMP 115.

Patient 10/Site 6

This 81-year-old white female had a history of CHF (NYHA Class II). Her medical history also included hypertension (10 years), aortic stenosis (1995), angina (January 1995), and syncope (May 6, 1997). The patient was admitted to the hospital on May 11, 1997 following an inferior myocardial infarction. The patient also had a critical aortic stenosis (0.5 cm²) and a severe ostial stenosis of the right coronary artery. On May 15, 1997, she received two 10 µL/kg doses of DMP 115, each given as a bolus. The patient had recurrent chest pain (chest pain) 4 days later (May 19, 1997) following a gastroduodenoscopy with junctional rhythm and was transferred to the Medical Intensive Care Unit. On May 21, 1997, the patient had episodes of atrial fibrillation (atrial fibrillation) and intermittent chest pain (chest pain). An acute myocardial infarction was ruled out, and the patient remained hemodynamically stable. On May 22, 1997, 7 days after dosing, the patient experienced three episodes of life-threatening bradycardia (bradycardia) within a half hour (each lasting for 1 minute). Approximately 5.8 hours after the last episode of bradycardia, she developed ventricular tachycardia (ventricular tachycardia) and ventricular fibrillation (ventricular fibrillation) followed by cardiac

arrest (cardiac arrest). Resuscitation efforts were unsuccessful. The investigator considered the death to be due to the patient's underlying severe cardiac disease and unrelated to DMP 115.

Study DMP 115-010

Patient 104/Site 2

This 66-year-old white male had a history of metastatic liver disease, colon cancer, CVA, carotid endarterectomy, hypertension, and diabetes mellitus (type II, borderline). On January 6, 1998, the patient received two doses of DMP 115 (30 μ L/kg followed by 10 μ L/kg; each given as a bolus injection). Two days later (January 8, 1998), the patient underwent lysis of adhesions, intraoperative hepatic ultrasound, and right hepatic lobectomy. On January 11, 1998, five days after dosing with DMP 115, the patient had a pulmonary embolus (pulmonary embolus) that resulted in death on the same day. The investigator considered the pulmonary embolus and resulting death unlikely to be related to DMP 115.

Patient 107/Site 1

This 66-year-old black male had a history of multiple liver lesions, small cell lung cancer, and extensive cardiovascular findings that included CAD, MI (1979, 1994), CHF, CABG, and hypertension. The patient was admitted to the hospital on April 27, 1998 and was treated for CHF and hypertension. On May 1, 1998, the patient received two doses of DMP 115 (30 μ L/kg followed by 10 μ L/kg; each given as a bolus injection). The patient began to have atrial fibrillation (atrial fibrillation/flutter) of mild intensity the following day (May 2, 1998) and underwent successful cardioversion on May 4, 1998. The patient went into severe cardiac failure (congestive heart failure) on May 10, 1998 that continued until May 13, 1998 and resulted in death. The investigator considered the cardiac failure and resulting death unlikely to be related to DMP 115.

Study DMP 115-903

Patient 1/Site 3

This 78-year-old white male entered Part A of the study with a history of an inferior wall myocardial infarction (MI) in April 1989 and a second inferior wall MI on November 20, 1996, 5 days prior to DMP 115 dosing, and received thrombolytic therapy. Other

cardiovascular history included atrial fibrillation, ischemic cardiomyopathy, hypertension, angina, volume overload, and an ejection fraction of 40-45%. On November 25, 1996, the patient received six bolus injections of DMP 115 in just under 1 hour: two doses of 100 μ L, two doses of 200 μ L, and two doses of 450 μ L (5.2 μ L/kg, instead of the planned 10 μ L/kg dose) for a total dose of 1500 μ L (17.2 μ L/kg). Additional information from the site indicated that the patient underwent a percutaneous transluminal coronary angioplasty (PTCA) on the day of DMP 115 dosing and had a coronary artery bypass graft (CABG) (five vessels) the following day (November 26, 1996). Clinical laboratory tests performed that day showed a decrease in hemoglobin, hematocrit, and red blood cell (RBC) count, and an increase in white blood cell (WBC) count with bands. The abnormal hematology values showed slight improvement at 48 and 72 hours after DMP 115 administration. On November 28, 1996, the patient began receiving packed RBCs.

The patient subsequently developed the following severe AEs: colitis (*Clostridium difficile* colitis) on December 2, 1996, uraemia (acute renal failure) on December 5, 1996, and pneumonia (pneumonia) and sepsis (sepsis) on December 6, 1996. The patient died on December 10, 1996 due to multisystem failure and sepsis. The investigator considered these events to be related to the patient's underlying clinical condition at trial entry and not related to DMP 115.

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APPENDIX D.2.2 - NARRATIVE SUMMARIES FOR SERIOUS ADVERSE EXPERIENCES OTHER THAN DEATH

Study DMP 115-902

Patient 45/Site A

This 66-year-old white male had a medical history of atrial fibrillation, Grade 2 heart failure, and alcoholism. At the screening physical examination, mild aortic and mitral regurgitation, and displaced apex beats were observed. In addition, the patient was receiving furosemide, digoxin, and enalapril for heart failure and warfarin for atrial fibrillation at baseline. The patient received a 5 $\mu\text{L}/\text{kg}$ dose of DMP 115 administered as an IV bolus. On July 12, 1996 (approximately 3 weeks after dosing), the patient experienced cardiac failure (exacerbation of heart failure) that was severe in intensity. The patient was hospitalized and his concomitant medications were changed (the furosemide dose was increased from 40 mg once a day, PO, to 80 mg twice a day, IV). The patient was also discontinued from the trial in response to this event. The cardiac failure was last recorded as ongoing, but the patient was discharged in stable condition after a 2-week hospital stay. The investigator considered the cardiac failure to be a progression of the patient's known Grade II heart failure and not related to DMP 115.

Patient 21

This 45-year-old white male was hospitalized prior to study entry, on April 14, 1998 for a suspected MI. On April 21, 1998, the patient underwent a successful PTCA and stenting of the right coronary artery, with a reduction of distal stenosis from 80% to 0%. He experienced atypical chest pain on April 22, 1998, prior to dosing with DMP 115. Later that day, the patient was infused with 2.6 mL of DMP 115 in 100 mL of normal saline (18.5 $\mu\text{L}/\text{kg}$); the total volume administered was 90 mL over approximately 57 minutes. Two days after dosing, on April 24, 1998, the patient experienced chest pain (chest pain) and was hospitalized for observation. MI was ruled out, and a stress test was performed April 26, 1998 without complication. The chest pain was recorded as mild in intensity, and resolved approximately 24 hours after dosing. The investigator considered the chest pain unlikely to be related to DMP 115.

Study DMP 115-004

Patient 1 Site 2

This 75-year-old white male received two 10 μ L/kg doses of DMP 115 (each given as a bolus) on March 25, 1997. Three days after dosing, on March 28, 1997, the patient was hospitalized for cardiac catheterization to evaluate his cardiac status. Following a review of the catheterization results, coronary artery bypass surgery was recommended. The patient remained hospitalized until bypass surgery could be performed. The investigator considered the coronary artery disease and resulting prolonged hospitalization for this patient to be unrelated to DMP 115.

Patient 5/Site 2

This 72-year-old white male received two 5 mL/kg doses of DMP 115 (each given as a bolus) on April 3, 1997. Twelve days after dosing, on April 15, 1997, the patient had a cholecystectomy performed for a pre-existing condition of cholelithiasis (gallstones). The procedure and related hospitalization were considered by the investigator to be unrelated to DMP 115.

Study DMP 115-005

Patient 1/Site 1

This 37-year-old white male had a history of diabetes, myocardial infarction (three times), percutaneous transluminal coronary angioplasty (two times), and placement of a coronary artery stent (two times). He received two 10 μ L/kg doses of DMP 115 (each given as a bolus) on March 25, 1997. On March 28, 1997 at the 72-hour follow-up visit (12:30 pm), he was observed to have no problems. Later that same day, the patient developed significant chest pain and was admitted to the Coronary Care Unit for evaluation. The patient was diagnosed as having a myocardial infarction (myocardial infarction), and on March 31, 1997, he underwent percutaneous transluminal coronary angioplasty of his stented vessel. The investigator considered the myocardial infarction to be related to the patient's underlying coronary artery disease and unrelated to DMP 115. The myocardial infarction resolved on April 1, 1997.

Patient 13/Site 5

This 70-year-old white male had a long history of cancer, including basal cell carcinoma, melanoma, and squamous cell carcinoma. In April 1996, the patient had renal cell carcinoma removed. On March 12, 1997, he received two 5 $\mu\text{L}/\text{kg}$ doses of DMP 115 (each given as a bolus). The patient was seen in the dermatology clinic for a routine follow-up visit and underwent a surgical excision of carcinoma (squamous cell carcinoma) on the dorsum of the left hand 7 days later (March 19, 1997). The cancer was considered to be unrelated to DMP 115. The patient continued to be followed by the dermatology clinic.

Study DMP-009

Patient 101/Site 8

This 43-year-old white male entered the study with a mass in the right lobe of his liver. On March 6, 1998, the patient received two doses of DMP 115 (30 $\mu\text{L}/\text{kg}$ followed by 10 $\mu\text{L}/\text{kg}$; each given as a bolus injection). The liver mass was treated by ablation on the same day. The following day, March 7, 1998, the patient began to have a fever (fever) of moderate intensity and abdominal pain (pain abd) of severe intensity for which he was hospitalized. A radiograph of the abdomen was performed, and the patient was treated with Ancef[®] (cefazolin), Flagyl[®] (metronidazole), Zantac[®] (ranitidine), and morphine. The fever resolved within 6 days and the abdominal pain was last recorded as ongoing. The patient failed to return for follow-up. The investigator considered the fever and abdominal pain unlikely to be related to DMP 115.

Patient 201/Site 11

This 77-year-old white male entered the study with a right kidney mass. His medical history included a lung mass (presumed malignant), extensive cardiovascular findings (myocardial infarctions [MI] in 1974 and 1987, coronary artery bypass surgery [CABG] in 1988, aortic graft in 1990, CHF, and hypertension), chronic renal failure (10 to 15 years), prostate cancer, and aplastic anemia (1985). In addition, the patient had a history of drug sensitivities to penicillin, anti-inflammatory drugs, and contrast dye. On March 3, 1998, the patient received two doses of DMP 115 (30 $\mu\text{L}/\text{kg}$ followed by 10 $\mu\text{L}/\text{kg}$; each given as a bolus injection). A biopsy of the kidney mass was performed 6 days after dosing on March 9, 1998. The patient developed right flank pain and was seen in the emergency room on March 12, 1998, at which time treatment with morphine

sulfate was initiated. On March 16, 1998, the patient was admitted to the hospital with moderate confusion (mental status changes secondary to a drug-related effect of morphine sulfate). The patient was treated with medication (medication not specified) and the mental status changes resolved on March 19, 1998. The investigator considered the confusion unlikely to be related to DMP 115.

Patient 203/Site 1

This 60-year-old white male entered the study with a left renal mass. On February 24, 1998, the patient received two doses of DMP 115 (10 μ L/kg followed by 30 μ L/kg; each given as a bolus injection). Fourteen days after dosing, on March 10, 1998, the patient had a total left nephrectomy performed for renal carcinoma (renal cell carcinoma). The investigator considered the procedure and the renal carcinoma unlikely to be related to DMP 115.

Patient 205/Site 8

This 60-year-old Hispanic female entered the study with renal artery stenosis (with stent) and hematuria. Her medical history included chronic obstructive pulmonary disease (COPD), pneumonia, basilar atelectasis, hypertension (1997), congestive heart failure (CHF; 1997), coronary artery disease (CAD), and cerebrovascular accidents (CVA; April and May, 1996). On April 30, 1998, the patient received two doses of DMP 115 (10 μ L/kg followed by 30 μ L/kg; each given as a bolus injection). Six days after dosing, on May 6, 1998, the patient began to have severe dyspnea (shortness of breath) for which she was hospitalized and given medication (medication not specified). The dyspnea resolved on May 11, 1998. The investigator considered the dyspnea unlikely to be related to DMP 115.

Study DMP 115-010

Patient 104/Site 1

This 65-year-old white male had a history of hepatitis C, hypertension, diabetes mellitus (type II), cirrhosis, and elevated liver function tests. On March 24, 1998, the patient received two doses of DMP 115 (10 μ L/kg followed by 30 μ L/kg; each given as a bolus injection). Two days after dosing (March 26, 1998), the patient underwent an exploratory celiotomy, lymph node biopsy, liver biopsy, and enteropathy with ultrasound. On that day, the investigator reported an AE of impaired healing (wound dehiscence), for which

the patient was hospitalized and treated with medication (medication not specified). The intensity of the event was recorded as mild and the event resolved on April 2, 1998. The investigator considered the event of impaired healing unlikely to be related to DMP 115.

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ON ORIGINAL**

APPENDIX D.2.3. - NARRATIVE SUMMARIES FOR SAFETY-RELATED DISCONTINUATIONS

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APPENDIX D.2.3 - NARRATIVE SUMMARIES FOR SAFETY-RELATED DISCONTINUATIONS

Study DMP 115-005

Patient 4/Site 3

This 42-year-old Hispanic male entered the study without any known allergies or drug sensitivities. On May 1, 1997, the patient received a single 10 $\mu\text{L/kg}$ dose of DMP 115, given as a bolus. Within 11 minutes after dose administration, the patient began to have increased sweating (cold sweats), dizziness (dizziness), blurry vision (abnormal vision), and nausea (nausea), all of moderate intensity. No treatment was given for any of the AEs, and within approximately 1 hour, all four had resolved. The patient was withdrawn from the trial and did not receive the planned second injection of DMP 115. The investigator considered the increased sweating, dizziness, abnormal vision, and nausea to be probably related to DMP 115.

Patient 15/Site 4

This 28-year-old Hispanic male entered the study without any known drug sensitivities, but was allergic to shellfish, feather down, cats, dogs, mold, mildew, insecticides, and bacteria. The patient also had a history of hay fever. On March 5, 1997, the patient received a single 10 $\mu\text{L/kg}$ dose of DMP 115, given as a bolus. Within 3 minutes after dose administration, the patient began to have urticaria (hives) and pruritus (pruritus), both of moderate intensity. Diphenhydramine was given to treat the AEs, and the urticaria and pruritus resolved within 24 hours. The patient was withdrawn from the trial and did not receive the planned second injection of DMP 115. The investigator considered the urticaria and pruritus to be probably related to DMP 115.

Study DMP 115-006

Patient 8/Site 3

This 31-year-old white male entered the trial with peritonsillar abscesses and sinusitis. No concomitant medications were reported. On October 15, 1997, the patient received a single 10 $\mu\text{L/kg}$ dose of DMP 115, given as a bolus. Within 2 minutes after dose administration, the patient complained of dizziness (dizziness) and appeared pale. At 3 minutes post-injection, his systolic blood pressure had increased by 20 mmHg and his

heart rate had increased by 15 beats per minute. This lasted approximately 5 to 10 seconds. An extra ECG was obtained and showed no change. Nine minutes after injection, the patient had another episode of dizziness with similar changes in blood pressure and heart rate that lasted approximately 10 seconds. The patient recovered quickly but was not given the second injection of DMP 115. At the 24-hour follow-up, the patient experienced a third episode of brief dizziness (reported as a feeling of drunkenness), which occurred while he was driving the previous evening (at 3:00 am October 16, 1997, ~9 hours after dosing). No additional episodes occurred, and the patient was symptom-free at follow-up. The investigator considered the events possibly related to DMP 115.

Study DMP 115-009

Patient 101/Site 5

This 46-year-old white male entered the study without any known allergies or drug sensitivities. His medical history included left ventricular hypertrophy, hypertension (15 years), and ulcerative colitis. On March 17, 1998, the patient received a single 30 μ L/kg dose of DMP 115, given as a bolus injection. Within 1 minute after dose administration, the patient began to have chest pain (chest pressure) and at 3 minutes dosing, he developed leg cramps (leg cramps) and pain (pelvic cramps). The chest pain was recorded as moderate in intensity, and the leg cramps and pain were recorded as severe in intensity. The chest pain resolved within 1 minute, the leg cramps and pain resolved within 12 minutes. The patient also had AEs of hypertonia (leg stiffness) and pain (groin pain) that were reported within approximately 45 minutes following the dose administration and resolved within approximately 2 minutes; these AEs were of mild intensity. Another episode of hypertonia occurred approximately 17 hours post-dose and resolved after 1 hour. All AEs resolved without treatment. The patient was withdrawn from the trial and did not receive the planned second injection of DMP 115. The investigator considered the chest pain, leg cramps, pain (pelvic cramps), hypertonia, and pain (groin pain) to be probably related to DMP 115.

Patient 104/Site 10

This 30-year-old white female had a history of drug sensitivity to Compazine® (prochlorperazine). Her medical history also included migraine headaches (21 years). On February 5, 1998, the patient received a single 30 μ L/kg dose of DMP 115, given as a bolus injection. Within approximately 15 minutes after dose administration, the patient

began to have abdominal pain (stomach tightness), dyspnea (shortness of breath), flushing (flushed face), and pruritus (itching at the tips of fingers and legs). These AEs resolved within 6 minutes. The patient developed a rash (red spot) on the side of her neck and conjunctivitis (red eyes) approximately 7 hours after the dose administration; these AEs resolved 4 days post-dosing. The intensity of the dyspnea was recorded as severe; the remaining AEs were moderate. All AEs resolved without treatment. The patient was withdrawn from the trial and did not receive the planned second injection of DMP 115. The investigator considered all of the AEs to be probably related to DMP 115.

Patient 203/Site 9

This 29-year-old white female had a history of drug sensitivity to codeine and decongestants. Her medical history also included hypertension. On January 5, 1998, the patient received a single 10 $\mu\text{L}/\text{kg}$ dose of DMP 115, given as a bolus injection. Within 3 minutes after dose administration, the patient began to have moderate dyspnea (respiratory distress) and severe chest pain (chest pressure). The dyspnea resolved within 9 minutes and the chest pain resolved within 7 hours, both without treatment. The patient was withdrawn from the trial and did not receive the planned second injection of DMP 115. The investigator considered the dyspnea and chest pain to be probably related to DMP 115.

Patient 207/Site 2

This 38-year-old white female had a history of multiple drug sensitivities, including contrast allergy (Renografin[®]; 1979). Her medical history also included a head cold and asthma. On May 12, 1998, the patient received a single 30 $\mu\text{L}/\text{kg}$ dose of DMP 115, given as a bolus injection. Within 1 minute after dose administration, the patient began to have headache (headache), flushing (face heavy, feels hot, and flush), nausea (nauseated), taste perversion (taste perversion), toothache (teeth hurt), chest pain (chest heavy), and paresthesia (hands icy). All AEs were recorded as mild to moderate in intensity. The patient was treated with Tylenol[®] (acetaminophen) and oxygen via a nasal cannula. All AEs resolved within 1.3 hours. The patient was withdrawn from the trial and did not receive the planned second injection of DMP 115. The investigator considered all events to be probably related to DMP 115.

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Study DMP 115-010

Patient 106/Site 13

This 58-year-old white female had a history of drug sensitivity to penicillin and sulfa. Her medical history also included hiatal hernia, cholecystectomy (1995), cirrhosis (1997), and anxiety. On January 8, 1998, the patient received a single 30 μ L/kg dose of DMP 115, given as a bolus injection. Approximately 4 minutes after dose administration, the patient began to have abdominal pain (epigastric pain), back pain (back pain), and pain (cramping), all of severe intensity. The patient was treated with oxygen, and the AEs resolved in 2.5 hours. The patient was withdrawn from the trial and did not receive the planned second injection of DMP 115. The investigator considered the abdominal pain, back pain, and pain to be probably related to DMP 115.

Patient 210/Site 1

This 51-year-old white male had a history of CAD, percutaneous transluminal coronary angioplasty (PTCA; 1992), arrhythmia, and hypertension. The patient did not have any known allergies or drug sensitivities. On May 18, 1998, the patient received a single 30 μ L/kg dose of DMP 115, given as a bolus injection. Approximately 5 minutes after dose administration, the patient began to have moderate chest pain (chest pain) that resolved within 1 minute without treatment. The patient was withdrawn from the trial and did not receive the planned second injection of DMP 115. The investigator considered the chest pain to be probably related to DMP 115.

Study DMP 115-017

Patient 17/Site 2

This 62-year-old white male had a history of bronchiectasis, double lobectomy, asthma, prior myocardial infarction, gallbladder removal, diabetes, hypercholesteremia, and had a known allergy to sulfa drugs. The patient was taking 11 concurrent medications, primarily for pulmonary and cardiovascular ailments. On August 27, 1998 the patient received a single 10 μ L/kg dose of DMP 115, given as a bolus injection. Approximately 1 minute after dose administration, the patient experienced severe back pain (back pain). No treatment was required, and the pain resolved within 15 minutes. The patient was discontinued from the trial and did not receive the planned second bolus injection (10 μ L/kg DMP 115) or the planned infusion administration (1.3 mL DMP 115 in 50 mL of saline). The investigator considered the back pain to be probably related to DMP 115.