

12 September 2011

Dr. Caleb Briggs  
Division of Advisory Committee and Consultant Management  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue  
WO31-2428  
Silver Spring, MD 20993-0002

**Re: Ferriprox® (deferiprone): 500 mg film-coated tablets (NDA 21-825)**  
**Addendum to FDA Backgrounder for ODAC meeting**

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Dear Dr. Briggs:

This letter is a follow-up to the FDA's notice that it will provide to the Advisory Committee Members on September 14<sup>th</sup> as an Addendum to the FDA Background Package. A component of that Addendum contains an assessment of the EIR for the clinical sites in Toronto of the LA-01 study. ApoPharma addressed the issues raised in the EIR as part of its response to the CRL submitted to the Agency in April, 2011 and has sent that portion of the CRL response to you for distribution. The document in the CRL included attachments that contain confidential patient and correspondent information, and these have been excluded from the document to be made public. However, the attachments can be made available to the Committee should they wish to explore the matter further.

We are including this redacted copy of the response, to be read in conjunction with the FDA's Addendum so that the reviewer may have a complete overview of the EIR and how ApoPharma has addressed questions raised in the EIR. This will supplement the information provided by the DSI, which appears to have stopped short of fully reviewing the response submitted by ApoPharma.

ApoPharma permits the FDA to release the document to the public.

Sincerely,



Michael Spino, B.Sc.Pharm., Pharm.D.  
President

cc. Ms. Nancy B. Sager

### Response to LA-01 FDA Inspection observations

The FDA Establishment Inspection Report (FEI 300761479) is unusual in many respects, including the fact that a large component of its "Background" section details Dr. Olivieri's views on matters of contention in the LA-03 study. Given that Dr Olivieri refused to permit her Co-Investigator, Dr Gideon Koren, any representative from the Hospital for Sick Children, or any representative from ApoPharma to be present during the introductory comments, as well as throughout the inspection and the close-out interview, the inspector was constrained in her access to information from a single source, Dr. Olivieri. Combined with the stated limitations in time for the conduct of the inspection, and the lack of access to source documents, it appears that the inspector was limited to input from Dr. Olivieri and her personal documents on matters that are contentious. A review of the inspection report reveals that much of the information presented to the inspector was not only contentious, but also incorrect or misrepresented. Comments are provided below on matters of potential relevance to the submission, as they relate to the safety and efficacy of Ferriprox, as challenged by Dr. Olivieri and presented in the EIR.

- **Page 1; Paragraph 1: High-Priority Inspection directed at obtaining documents regarding the investigator's concerns of hepatic fibrosis and a loss of efficacy over time.**

In light of this being designated a High-Priority inspection, it is unclear why there appears to have been no attempt to obtain definitive and objective information during the inspection that might corroborate or refute the information presented by Dr. Olivieri. The following specifies some of the matters that would have been relevant to pursue if this were a high priority inspection regarding matters pertaining to concerns of hepatic fibrosis and loss of response raised by Dr. Olivieri:

- This is a very old matter in that the investigator's concerns were raised 12 years prior to the inspection and the documentation supporting those concerns are about 20 years old, as asserted by the Inspector. The investigator's concerns have been reported by the Sponsor to the Agency, namely in its [REDACTED]. It was clear from these communications that one of the investigators was at odds with the sponsor, with her co-investigator, other investigators and with panels convened to address the specific matters. Furthermore, there is a body of published literature addressing the investigator's concerns (references provided with the below discussion) and they are consistent that deferiprone is not associated with a worsening of hepatic fibrosis or loss of response. Twenty-three years of clinical experience with deferiprone provide evidence that long-term deferiprone use is not associated with a loss of its efficacy.
- This inspection could have served as an ideal opportunity to obtain factual information that could have brought closure to the issue for the FDA, in the event that the FDA had not yet accepted the widespread view of the medical and scientific community at large on the issue of liver fibrosis and loss of response issues (references provided with the below discussion). Instead the EIR reiterates the views of one investigator without any

evidence that the Inspector attempted to be discriminating or even assess the investigator's views against any counter evidence.

For easiness of the review, a summary of the investigator's concerns and how they were addressed by the Sponsor is provided herein.

- **Page 1; Paragraph 1: Investigator's concerns of hepatic fibrosis.**

At no time during the conduct of either LA-01 or LA-03, did Dr. Olivieri ever advise ApoPharma that she suspected that deferiprone might be associated with the development of hepatic fibrosis. These apparent concerns were first raised well after the termination of the study. On 22 January 1997, 8 months after study LA-03 had been terminated, ApoPharma Inc. was sent a copy of a report prepared by Dr. Olivieri where she raised concerns that deferiprone exacerbated liver fibrosis. Although the study was not conducted in the USA or under an IND, the report was addressed to the US FDA. In the report, Dr. Olivieri reported progression of liver fibrosis in patients treated with deferiprone in study LA-03. Upon receipt of Dr. Olivieri's report, ApoPharma sent a copy of it to all investigators participating in the ApoPharma Ferriprox clinical studies. At the time, ApoPharma was sponsoring study LA-02/06 and ApoPharma asked the investigator in all study sites to review the information presented by Dr. Olivieri and reference her claims in the consent forms provided to all patients participating in the ApoPharma Ferriprox study. An addendum to the informed consent was provided to and signed by the study participants to include and acknowledge Dr. Olivieri's claims. ApoPharma also convened an *Ad Hoc* meeting of the Safety Committee that oversees the safety of patients enrolled in the Ferriprox studies. The Committee recommended a review of the liver biopsy slides on which Dr. Olivieri had based her claims. The slides were reviewed in a randomized and blinded fashion by an independent hepatopathologist, using 2 different scoring systems, and his assessment revealed that there was no progression of liver fibrosis when all of the slides were reviewed. The pathologist further noted that most of the specimens were inadequate to allow firm conclusions, but if one were to disregard the quality of the material and assessed all the slides, one would find an overall decline in liver fibrosis, not a progression. A copy of the [REDACTED] was provided to the Agency on 13 August 1997. A copy of the [REDACTED] was also provided to Dr. Olivieri.

In 1998, Dr. Olivieri published her claims.<sup>(1)</sup> No acknowledgement was made that the slides had been reviewed by another hepatopathologist and that his results differed from hers.<sup>(2)</sup> Without having seen the other pathologist's report, the editorial that accompanied Dr. Olivieri's publication also identified important design deficiencies in this study, such as the evaluation of biopsy samples normally considered too small to be adequate, the lack of a true control population, and the presence of other factors, such as infectious hepatitis and liver iron overload which are known to influence the progression of fibrosis.<sup>(3)</sup>

Since that time, a body of independent studies assessed liver histology during therapy with deferiprone. Those studies, which include the review of the biopsies of patients enrolled in the ApoPharma studies LA-02/06 that was commissioned by the Safety Committee, are summarized in [REDACTED]. They are consistent in their results that deferiprone use is not associated with exacerbation of liver fibrosis.

- **Page 1; Paragraph 1: Investigator's concerns of loss of response.**

In August 1995, Dr. Olivieri informed ApoPharma that her review of the LA-03 data indicated a loss of efficacy in several patients. Dr. Olivieri presented Apotex with graphical representation of the data and informed ApoPharma of her intention of submitting her interpretation of the data to her IRB. As the data those graphs were based upon had not been provided to ApoPharma at that time, the company asked Dr. Olivieri to provide the data upon which her conclusions were drawn. These data were subsequently provided in a spreadsheet format. The spreadsheet contained discrepancies with those recorded on the study case report forms (CRF's) and ApoPharma reported these discrepancies to her. A data set was finalised by Dr. Olivieri in February 1996 and provided to ApoPharma. ApoPharma reviewed these data and concluded that they did not support a loss of efficacy.

To further evaluate the question of loss of efficacy, ApoPharma submitted to the investigators participating in study LA-02 the dataset provided by Dr. Olivieri. Their interpretation of the data was that there was no evidence to support a loss of efficacy over time.

ApoPharma also convened an independent Expert Review Panel to review the dataset. Contrary to Dr. Olivieri's claim (Inspection Report, Page 5, last sentence), the Panel was provided all data supplied by Dr. Olivieri in February 1996 and all relevant information available to ApoPharma for studies LA-01 and LA-03 at the time. For study LA-01, which was a comparative study, the Panel was blinded with respect to the treatment groups and patient randomization. The panel was asked to determine if they considered that there was an unexpected response and/or a lack of efficacy with continued deferiprone treatment in either study. The Panel consisted of two hematologists with international expertise in thalassemia. The other two members were a biostatistician and a pediatric clinical pharmacologist. In June 1996, Dr. Olivieri provided additional information, which was also forwarded to the Review Panel. The following is a summary of the key conclusions in the report prepared by the Review Panel:

1. Specifically, the committee does not find a trend toward a loss of effectiveness of therapy in patients treated with deferiprone on a long-term basis. There are no sudden, unexpected changes in regard to failure of therapy.
2. There does not appear to be any difference at this point between the clinical results with deferiprone and deferoxamine (DFO) under the terms of the study.

A copy of the Panel's report was provided to the FDA on 17 October 1996 and to Dr. Olivieri. In 1998, Dr. Olivieri published a manuscript in the NEJM,<sup>(1)</sup> which concluded that deferiprone use was associated with a loss of efficacy. No acknowledgment was made in the publication that the data had been reviewed by other investigators and by a third party panel, both of which assessed there was no evidence of a loss of response over time.

The results of the ApoPharma sponsored studies are consistent with those of independent investigations on the long-term therapy with deferiprone that there is no loss of efficacy over

time but most important, long term deferiprone therapy is associated with reduced morbidity and mortality compared to deferoxamine.<sup>(4-14)</sup>

- **Page 1; last Paragraph: “No significant site compliance issues were noted in the correspondence files”**

██████████ contains samples of communications submitted by ApoPharma regarding significant site compliance issues. In light of the fact that the NDA included reference to important protocol violations ██████████ notes that Study LA-01 was terminated because of investigator non-compliance. ██████████

██████████, it is unclear why the inspection did not pursue this matter when the PI apparently failed to produce such correspondence.

There were a large number ██████████ of communications between the sponsor and the site addressing concerns in the conduct of the study, as early as 1994 ██████████ is a copy of an audit report provided to Dr. Olivieri). In fact, based on these concerns, the sponsor conducted an In-service training on Good Clinical Practice (GCP) on 29 Jun 1995 ██████████ to the site personnel.

- **Page 4; Paragraph 2: “This inspection included a limited review of fifteen subject files against data in the tables and verification of forty-five (45) liver biopsy pathology reports from twenty-one (21) patients at the Hospital For Sick Children.”**

It is unclear to ApoPharma if the 45 liver biopsy pathology reports from 21 patients at the Hospital for Sick Children refer to patients in study LA-01 or study LA-03. In her 1997 report submitted to the FDA and copied to ApoPharma, Dr. Olivieri provided 66 fibrosis scores from 21 patients in study LA-03, which are summarized in Table 1.

**Table 1. Fibrosis score reported by investigator in the 1997 report**

PT INITIALS	YEAR START DEFERIPRONE	1988	1989	1990	1991	1992	1993	1994	1995	1996
	1993					3.0			3.0	3.5
	1993						3.0		3.0	
	1989			2.5	2.5	3.0				
	1989			0.0	2.0	3.0	3.0	3.0		
	1994	<i>no reports on biopsies on 11/2/93 and 14/10/93</i>								
	1991				4.0	4.0				
	1990			3.0	3.0	3.0	3.5	3.5		4.0
	1990			3.5	3.5	3.5		4.0		4.0
	1990			4.0	4.5	4.5	4.5			4.5
	1991				3.0	3.5	3.5	3.5		
	1991				3.0	3.5		3.5		
	1989			2.5	2.5	3.0				
	1990			2.5	3.0	3.0		4.0		
	1993	<i>no reports on biopsies on 17/12/92 and on 9/12/95</i>								
	1993						3.0	4.0	4.0	
	1991				2.5	3.0	3.0		3.5	
	1990			3.0	3.5	3.5	3.5	4.0		
	1991				3.0		3.0			
	1992					4.0	4.0	4.0		
	1990			0.0	3.0	3.0				
	1991				3.0			4.0		

A copy of liver fibrosis scores from patients treated with deferiprone as part of the randomized study LA-01 that were provided by Dr. Olivieri to the European Court of Justice in April 1999 was provided to ApoPharma in 2003. Although liver biopsies were also carried out for deferoxamine (DFO)-treated patients in the LA-01 study, ApoPharma was not provided access to the fibrosis score of DFO-treated patients in this randomized study. Presumably, these were available to the Inspector and could have served as a reference point to any reported changes in deferiprone patients, since this was a randomized study.

It appears that the inspection involved a review of summary tables from the investigator's own files, as opposed to an independent review, as chosen by the Inspector of original records.

- **Page 6: "Additional background information is provided in the Olivieri Report"**

The "Olivieri Report" is a document prepared by the union that supports university teachers, the Canadian Association of University Teachers (CAUT). It was based on information provided by Dr. Olivieri, but had no input from the Hospital for Sick Children, nor the University of Toronto, nor ApoPharma. ApoPharma is of the opinion that this report cannot be considered as unbiased background information.

- **Page 7: “Dr. Gary Brittenham, Case Western University, performed all SQUIDs and Liver Iron Concentrations (LIC) from biopsy samples in Cleveland, Ohio.”**

This is an erroneous statement. According to the protocol, assay of liver iron concentration from biopsies was to be conducted in the laboratory of Dr. D.M, Templeton (Department of Clinical Biochemistry, University of Toronto) to ensure uniformity of assessment. Partway through the study, there was a switch to Dr Brittenham at Case Western University.

- **Page 7: “All original LIC and SQUID records reside with Dr. Brittenham.”**

Presumably, the original LIC and SQUID records referred to by the Inspector are source documents. As noted by the Inspector, she was unable to access these source documents. Similarly, although requested, they were never provided to ApoPharma. Evidence that such was requested is found in [REDACTED]

- **Page 8: “Data Verification: A comparison of the data supplied with the assignment against data summaries prepared by the investigator raised a number of questions regarding the Sponsor’s criteria for inclusion and exclusion of data. Specifically, the sponsor’s data set excludes in their entirety twenty-nine (29) (or 45%) of the sixty-four (64) treated subjects.”**

On the basis of what is described in the EIR, it appears that the Inspector may have provided the investigator with confidential data submitted by ApoPharma in its IND, without authorization from ApoPharma, without a representative of ApoPharma being present, and knowing that the investigator was hostile to the interests of ApoPharma. This matter needs to be examined further. However, for the purpose of this document, we will not address this apparent violation, per se, any further, but will provide information relevant to concerns expressed by the Inspector.

Categorically, ApoPharma confirms that it provided all data available to it and reported the results in documents based upon both an “intention-to-treat” and a “per-protocol analysis”.

It is difficult for ApoPharma to address the Inspector’s questions on her comparison of the data that was supplied to her by the Agency against data summaries prepared by the investigator, as ApoPharma is unaware of the summaries prepared by the investigator. However, it is important to clarify that a total of 71 of the 75 patients enrolled in study LA-01 received study therapy, as 7 additional patients were from another study site. All study data on the 71-treated patients which were provided to the sponsor on study LA-01 Case Report Forms (CRFs) were provided [REDACTED]

The relative efficacy of deferiprone and DFO was assessed by comparing the change in liver iron concentration (LIC) from baseline to Month 24 between the two therapies (per protocol analysis). Because LIC was assessed by different methods (SQUID or biopsy) during the study, the following analyses were conducted, as described in section 7.1.3 of the LA-01 Clinical Study Report:

- a. combined data as measured by SQUID (preferentially) and biopsy
- b. combined data as measured by biopsy (preferentially) and SQUID
- c. SQUID data alone
- d. Biopsy data alone

An 'intent to treat' analysis was also carried out on the combined data by SQUID (preferentially) and biopsy, on the SQUID data alone and, separately, on the biopsy data alone, where the relative efficacy of the two regimens was assessed by comparing the change in liver iron concentration from baseline to Month 24 and Month 36, respectively.

Reasons for exclusion of any data point were detailed in the LA-01 Clinical Study Report provided to the Agency, in section 12.1.9 Documentation of Statistical Methods namely 24-Month Completer Analysis — Appendix 2.2.2 Data Excluded from Analysis of Liver Iron Concentration as Measured by Biopsy (Preferentially) and SQUID and 24-Month Completer Analysis — Appendix 2.2.3 Data Excluded from the Completer Analysis of Liver Iron Concentration as Measured by Biopsy (Preferentially) and SQUID Due to < 24 Months of Therapy. Additionally, assessments that were not completed can be found in the LA-01 Clinical Study Report, Section 12.2.2.2.

The FDA Establishment Inspection Report (FEI 300761479) indicates the following tables from the LA-01 Clinical Report were examined:

- a. Patient Listing of Discontinued Patients (12.2 Patient Data Listings)
- b. 24-Month Completer Analysis Appendix 2.2.1 Liver Iron Concentration Data Analyzed as Measured by Biopsy (Preferentially) and SQUID (21.1.9 Statistical Methods)
- c. 24-Month Completer Analysis — Appendix 2.2.2 Data Excluded from Analysis of Liver Iron Concentration as Measured by Biopsy (Preferentially) and SQUID (21.1.9 Statistical Methods)
- d. 24-Month Completer Analysis — Appendix 2.2.3 Data Excluded from the Completer Analysis of Liver Iron Concentration as Measured by Biopsy (Preferentially) and SQUID Due to < 24 Months of Therapy (21.1.9 Statistical Methods)

The tables examined during the inspection represent only one of the analyses described in the protocol, i.e. patients who completed 24 months of therapy on the study. As per section 7.4.1.1 in the Clinical Study Report, Liver Iron Concentration - Combined SQUID

(preferentially) and Biopsy Analysis: Thirty-nine patients are included in this analysis. Data from 5 of the 71 patients enrolled in the study were excluded from the per protocol analysis due to no baseline measurement within the 12 months prior to or 6 months after the start of study medication; data from 21 other patients were excluded due to no follow up measurements; data from 6 patients were excluded from the per protocol analysis since they did not complete 24 months of therapy for various reasons. Twenty-six of the remaining 39 patients who completed 24 months of therapy had liver iron concentration measurements at Month 24 (13 in each group). A complete list of patients excluded from this analysis is [REDACTED]

As stated in the FDA Inspection Report, "most data in the tables was verified against data summaries maintained by the investigator and not against the original records which were transferred elsewhere for copying". The limitations of using an investigator's summary data when conducting a valid assessment of claims of missing data are well-known to the Agency and will not be addressed here.

Although the Sponsor has not been provided the summary data tables that were presented by Dr. Olivieri to the Inspector, the Sponsor checked the data from the CRFs and the data which were filed in the submission and compared those data with the data from the summary tables as presented in the Data Verifications section of the FDA Inspection Report (subdivided by concern). This process revealed the source of the discrepancies raised in the EIR, as noted below.

**a) Page 8: "Specifically, the sponsor's data set excludes in their entirety twenty-nine (29) (or 45%) of the sixty-four (64) treated subjects"**

All LA-01 study data available to ApoPharma have been included in the clinical study report and corresponding case report tabulation datasets. The data set, as noted above, includes 71 patients, 64 of which were from the Toronto study sites. It is unclear how the EIR could refer to 29 missing study subjects, even if the Inspector relied on the summary prepared by the investigator.

**b) Page 8: "Additional long-term efficacy information (not found in the tables) was available for twenty-four (24) of the thirty-five (35) which remain"**

ApoPharma is not aware of what additional long-term information the investigator made available to the Inspector. ApoPharma is aware that Dr. Olivieri chose to continue treating some of the patients with Ferriprox, under the Special Access Programme of Health Canada, after the study was terminated, but do not know her criteria in selecting those patients. ApoPharma assumes the information provided was from the assessments conducted by the investigator in that subset of patients, after ApoPharma terminated Study LA-01 in May 1996. She reported such information in an abstract at the ASH meetings in December 1996<sup>(15)</sup> and in December 1997.<sup>(16)</sup> Although the information was not part of LA-01, ApoPharma reported it to the agency on [REDACTED] and [REDACTED] as part of the respective [REDACTED]

- c) **Page 8: “Some subjects with ten to thirty-five months of data were noted by the sponsor as excluded because less than twenty-four (24) months of data was available yet others with as few as eight (8 months) of data appear in the twenty-four (24) month analyzed data set.”**

It appears that the Inspector’s statement refers to the “Per Protocol” data set. In the “Per Protocol” analysis, the relative efficacy of DFO and deferiprone was assessed by comparing the change in liver iron concentration from baseline to Month 24 between the two therapies. For the ‘Per Protocol’ analysis, assessments occurring after the date of switching from deferiprone to DFO therapy for deferiprone patients, or assessments occurring greater than 6 months after the last study medication were excluded from the analyses.

As described in section 7.4.1.1 of the LA-01 Clinical Study Report, 39 patients were included in the “Per Protocol” analysis. Data from 5 of the 71 patients exposed to study therapy were excluded from the per protocol analysis due to no baseline measurement within the 12 months prior to or 6 months after the start of study medication; data from 21 other patients were excluded due to no follow up measurements; data from 6 patients were excluded from the per protocol analysis since they did not complete 24 months of therapy for various reasons. Twenty-six of the remaining 39 patients who completed 24 months of therapy had liver iron concentration measurements at Month 24 (13 in each group).

- d) **Page 8: “Some excluded subjects had a baseline assessment within twelve (12) months of randomization but not within twelve (12) months of the first dose. These subjects continued on for the duration of the study. The sponsor did not notify the investigator of this protocol deviation and call for a baseline within six months (the close of the baseline window) nor were they excluded prior to completion.”**

This information is incorrect. Perhaps a copy of the Study LA-01 Protocol was not provided to the Inspector and perhaps she was provided incorrect information by the investigator. The LA-01 protocol states that “The liver biopsies and the other pre-trial assessments must be performed within the 6 months preceding the initiation of therapy in this study” (emphasis added). Subsequently, protocol modification #5 was implemented so that assessments performed within 12 months of therapy initiation were accepted. In spite of that, the investigator enrolled 12 patients using baseline liver biopsy values performed 13 to 16 months prior to study entry. The investigator was made aware of these protocol violations, discovered during routine monitoring visits, both verbally and in writing, as documented above in the comment to the observation on the last paragraph of page 1 of the Inspection Report (“No significant site compliance issues were noted in the correspondence files”).

- e) **Page 8: This inspection found that much of the greater than twenty-four (>24) month data was available because it was obtained in the normal course of following these patients when they stayed on the investigational drug through Emergency Drug Release (Compassionate Use) Program (Exhibits 4.474-4.475). Two year data that was not submitted by the sub-investigator in the case report forms at the time**

**of closeout was reportedly offered or provided to the sponsor on subsequent occasions in the protracted legal battles between the sponsor and investigator (Exhibits 4.452-4.473).**

The Inspector is correct that the results of some assessments conducted post termination of the trial were provided to the sponsor "*on subsequent occasions in the protracted legal battles between the sponsor and investigator*", following the investigator's publication of the data. Those results, obtained outside of the clinical study, were not included in the analysis of the study data. Nonetheless, a copy of the two abstracts<sup>(15,16)</sup> that were published by the investigator presenting data in a subset of the study patients and which included data collected outside of the clinical trial have been provided by the sponsor to the agency in the [REDACTED] and [REDACTED]. ApoPharma has been denied access to the source documents upon which those abstracts have been prepared.

- f) Page 8: Additionally, subjects who were removed from the study as a result of treatment failures or adverse events within the first twenty-four (24) months appear to have been excluded from analysis. The treatment of them and subjects who were not able to complete the study because of its early termination were inconsistently addressed in the discontinued and excluded data sets. For example, subjects included in twenty-four (24) month completer analysis with final values between eight (8) and sixteen (16) months appear in the following table:"

Establishment Inspection Report	FEI:	300761479
Nancy F. Olivieri, M.D., Clinical Investigator	EI Start:	07/06/2009
Toronto, Ontario, Canada	BDW	EI End:
		07/10/2009

Subject #	Treatment	Baseline Date	Iron Date	Method	Sponsor's Value	PI's Value	Exhibit #	Baseline to Liver Iron (Months)
8	DFC	1/28/1994	4/2/1994	Biopsy	3.7	3.70	69.33	-9
8	DFC	1/28/1994	5/3/1994	Biopsy	5.3	5.30	69.33	16
10	DFC	12/2/1993	12/3/1993	Biopsy	4.67	4.70	69.16	-12
10	DFD	12/2/1993	11/9/1994	SQUID	4.37	4.40	69.33	11
25	DFC	12/21/1993	1/10/1994	Biopsy	7.73		69.10	-11
25	DFC	12/21/1993	12/1/1994	Biopsy	14.6		69.10	12
31	DFC	11/18/1993	1/26/1994	Biopsy	9.14	9.20	69.32	-10
31	DFC	11/18/1993	3/23/1994	Biopsy	23.7	23.70	69.32	16
34	DFC	3/24/1994	4/12/1994	Biopsy	9.8	9.80	69.18	-11
34	DFC	3/24/1994	11/16/1994	SQUID	9.99			8
37	DFC	11/24/1993	6/24/1994	Biopsy	15.52	15.70	69.37	-5
37	DFC	11/24/1993	3/6/1994	Biopsy	18.6	18.60	69.37	16
12	L1	10/8/1993	12/3/1993	Biopsy	20.68	20.70	69.17	-10
12	L1	10/8/1993	10/19/1994	SQUID	12.83			12
35	L1	11/30/1993	3/31/1994	Biopsy	4.8	4.80	69.20	-8
35	L1	11/30/1993	3/21/1994	Biopsy	3.5	3.50	69.33	16
59	L1	1/13/1994	5/7/1994	Biopsy	21.10		69.22	-8
59	L1	1/13/1994	11/16/1994	SQUID	16.40	16.38		10

As previously noted, the rationale for inclusion and exclusion of any data was specified in the protocol and followed consistently.

All patients listed in this table had  $\geq 24$  months of study drug exposure and thus were included in the "Per Protocol" analysis of LIC SQUID over liver biopsy. Perhaps the Inspector was not provided the following appendices which were submitted to the Agency as part of the LA-01 Clinical Study Report, which provide details on exclusion of data from the "Per Protocol" analysis:

- [REDACTED] Data Excluded from the Completer Analysis of Liver Iron Concentration as Measured by Biopsy (Preferentially) and SQUID Due to <24 Months of Therapy (12.1.9 Statistical Methods).
- Appendix of Protocol Deviations, Assessments not completed [REDACTED]

It is unclear to ApoPharma why the "PI's Value" is missing for study subjects # 25, 34, 12 and 59.

g) Page 9: Subjects with >8 months of data who were excluded from analysis on the basis of less than 24 months of data include:

Subject #	Treatment	Baseline Date	Liver Iron Date	Method	Sponsor's Value	PI's Value	Ex #	Baseline to Liver Iron (Months)	Comments
42 [REDACTED]	DFO	11/24/1993	6/24/1993	Biopsy	15.52			-5	
42 [REDACTED]	DFO	11/24/1993	6/8/1994	SQUID	4.3	4.30	69.29	7	
42 [REDACTED]	DFO	11/24/1993	3/6/1995	Biopsy	18.6			16	Included in 24 mo
42 [REDACTED]	DFO	11/24/1993	12/12/1995	Biopsy				25	
42 [REDACTED]	DFO	11/24/1993	10/30/1996	Biopsy		7.605	69.39	35	
43 [REDACTED]	DFO	11/16/1994	1/12/1994	Biopsy	8.9	9.50		-10	
43 [REDACTED]	DFD	11/16/1994	2/2/1994	SQUID	11.3			-9	
43 [REDACTED]	DFD	11/16/1994	9/6/1995	SQUID	6.1			10	SAE
43 [REDACTED]	DFO	11/16/1994	6/14/1996			5.328	69.40	19	
51 [REDACTED]	DFO	11/8/1993	11/20/1992	SQUID	9.98	10.10	69.12	-12	
51 [REDACTED]	DFD	11/8/1993	12/10/1992	Biopsy	9.98			-11	
51 [REDACTED]	DFO	11/8/1993	9/1/1994	Biopsy	7.9		69.29	10	SAE
51 [REDACTED]	DFO	11/8/1993	11/9/1994	SQUID	7.3		69.28	12	
55 [REDACTED]	DFO	10/21/1993	10/8/1992	SQUID	7.42	6.10	69.27	-12	
55 [REDACTED]	DFO	10/21/1993	10/29/1992	Biopsy	2.65	2.70	69.27	-12	
55 [REDACTED]	DFO	10/21/1993	11/3/1994	Biopsy	5.40	5.90	69.27	13	

All patients in this table had <24 months of exposure and were therefore excluded in the "Per Protocol" analysis of SQUID over liver biopsy. Please refer to the LA-01 Clinical Study Report, section [REDACTED]

[REDACTED] which addresses the exclusion of data from the analysis. It is important to clarify that all of these patients were included in the "Intent-to-treat" analysis.

It is unclear to ApoPharma why the "PI's Value" is missing for study subjects # 42, 43 and 51. It is also unclear to ApoPharma the reason for the difference between the "Sponsor's Value" and the "PI's Value" for subject #43 (8.9 vs. 9.5) and subject #55

(7.42 vs. 6.10). The "Sponsor's Value" are those provided by the investigator on the CRFs.

h) Page 10: Subjects excluded from analysis because the trial ended early (1996) include the following:

Subject #	Treatment	Baseline Date	Liver Iron Date	Method	Sponsor's Value	PI's Value	Exhibit #	Baseline to Liver Iron (Months)
44	L1	9/20/1995	7/19/1995	SQUID	1.9	1.87	47.4	-2
44	L1	9/20/1995	7/25/1995	Biopsy	1.4	1.40	47.2	-2
44	L1	9/20/1995	6/12/1996	Biopsy		3.99	47.2	9
44	L1	9/20/1995	6/19/1997	Biopsy		8.10	47.1	21
45	L1	9/20/1995	8/25/1995	Biopsy	2.4	2.40	46.1	-1
45	L1	9/20/1995	9/8/1995	SQUID	3.4	3.41	48.4	0
45	L1	9/20/1995	12/10/1996	Biopsy		8.60	69.38	15
46	DFO	9/20/1995	5/3/1995	Biopsy	4.1		69.32	-4
46	DFO	9/20/1995	7/19/1995	SQUID	4.1			-2
46	DFO	9/20/1995	11/20/1996	Biopsy		7.40	69.38	14
47	DFO	9/25/1995	4/4/1995	Biopsy	3.8	3.80	69.32	-5
47	DFO	9/25/1995	9/8/1995	SQUID	5.2			0
47	DFO	9/25/1995	4/3/1997			7.90		19
48	DFO	9/20/1995	6/3/1995	Biopsy	4.1		69.32	-4
48	DFO	9/20/1995	7/19/1995	SQUID	5.2			-2
48	DFO	9/20/1995	11/26/1996			8.545	69.38	14
49	L1	9/21/1995	6/30/1995	Biopsy	2.4		69.7	-3
49	L1	9/21/1995	6/13/1996	Biopsy		4.60	52.1	9
49	L1	9/21/1995	3/14/1997	Biopsy		14.87	69.38	18
50	DFO	9/20/1995	7/4/1995	SQUID	9.5	9.50	69.7	-2
50	DFO	9/20/1995	11/5/1996	Biopsy		14.14	69.38	14
63	L1	4/13/1995	1/10/1995	Biopsy	4.70	5.20	69.25	-3
63	L1	4/13/1995	1/18/1995	SQUID	4.93	4.93	64.3	-3
63	L1	4/13/1995	5/23/1996	Biopsy		4.40	69.25	13
63	L1	4/13/1995	5/22/1997	Biopsy		4.20	64.1	25
65	DFO	9/18/1995	8/31/1995	Biopsy	3.1	3.10	69.9	-1
65	DFO	9/18/1995	9/8/1995	SQUID	4.8	4.80	69.9	0
65	DFO	9/18/1995	Nov-97			2.55		28
66	L1	9/20/1995	7/24/1995	Biopsy	8.2	8.20	66.1	-2
66	L1	9/20/1995	6/28/1996	Biopsy		6.00	66.1	9
66	L1	9/20/1995	3/4/1997	Biopsy		7.00	69.39	18
67	L1	9/26/1995	6/22/1995	Biopsy	15.2	15.20	69.8	-3
67	L1	9/26/1995	7/19/1995	SQUID	13.2	13.20	67.3	-2
67	L1	9/26/1995	6/26/1996	Biopsy		12.18	67.1	9
67	L1	9/26/1995	3/27/1997	Biopsy		19.60	69.39	18
68	DFO	9/20/1995	7/19/1995	SQUID	7	7.0	69.9	-2
68	DFO	9/20/1995	8/28/1995	Biopsy	7.2		69.9	-1
68	DFO	9/20/1995	Dec-96	Biopsy		6.40	69.38	15

Only data received on the LA-01 CRFs up to the time of the close out visit were included in the analysis; none of these patients had follow up assessments or exposure  $\geq 24$  months. The data referred to in the investigator's table as collected when patients were on EDR are not applicable to the LA-01 Clinical Trial.

It is unclear to ApoPharma why the "PI's Value" is missing for study subjects #46, 47 and 48. It is also unclear to ApoPharma the reason for the difference between the "Sponsor's Value" and the "PI's Value" for subject #63 (4.70 vs. 5.20). The "Sponsor's Value" is that provided by the investigator on the CRF.

**i) Page 11: The following excluded data points that were in (the investigator's) opinion evaluable and favourable to DFO:**

Subject #	Baseline Date	Liver Iron Date	Method	Sponsor's Value	Investigator's Value	Exhibit #	Months from Baseline to Liver Iron
1	2/10/1994	10/19/1995	Biopsy	7.4		62	20
3	12/2/1993	2/8/1996	Biopsy	3.5	3.50	81	26
9	1/28/1994	7/18/1996			3.41		30
20	11/24/1993	10/22/1996	SQUID	6		69.47	36
34	3/24/1994	8/21/1996	Biopsy		1.70	69.36	29
43	11/16/1994	8/14/1996			5.30	69.40	19
46	9/20/1995	11/20/1996	Biopsy		7.40	69.36	14
47	9/25/1995	4/3/1997			7.90	69.39	19
51	11/8/1993	9/1/1994	Biopsy	7.9		69.26	10
55	10/21/1993	11/3/1994	Biopsy	5.40	5.90	69.27	13
65	9/18/1995	Nov-97			2.55		26
68	9/20/1995	Dec-96	Biopsy		5.40	69.36	15

No data were excluded based on whether or not the results were favorable or unfavourable to a study therapy. Subjects # 1 was excluded because he/she had no baseline values within 12 months prior to or 6 months after the start of study medication, as required in the study protocol. Subject # 3 was included in the ITT "Squid preferentially" analysis as he/she had a post baseline SQUID value that was back populated for baseline. For subjects # 9, 20 and 34, the values provided by the investigator were obtained approximately 2 to 18 months after trial termination. Subjects # 46, 47, 65 and 68 were excluded from the analysis as no post-baseline values were obtained during the study. For the other 3 subjects (subjects #43, 51 and 55), the values were excluded from the "Per Protocol" analysis because the patients did not have exposure  $\geq 24$  months. However, the values for those 3 patients were included in the "Intent-to-treat" analysis.

It is unclear to ApoPharma why the "PI's Value" is missing for study subjects # 1, 20 and 51.

## j) Page 12: The excluded data in this table was judged by the investigator to represent unfavourable outcomes for L1:

Subject #	Baseline Date	Liver Iron Date	Method	Sponsor's Value	Investigator's Value	Ex #	Months from Baseline to Liver Iron	comments
4	11/25/1993	6/19/1996	Biopsy	11.7	11.60	9.1	31	No source
5	11/23/1993	3/12/1997	Biopsy		18.10	69.38	40	
6	12/6/1993	5/28/1997	Biopsy		21.12	69.40	41	
11	11/23/1993	3/13/1997			12.80	69.38	40	
12	10/8/1993	7/16/1996	Biopsy		6.50	69.40	33	Unfavorable due to ↑ALT results
14	12/8/1993	3/14/1997	Biopsy		9.40	69.38	39	
15	11/19/1993	6/11/1996	Biopsy	13	17.80	20.1	31	Included but with CRF error; no available source doc for PI's data
17	12/0/1993	5/21/1997	Biopsy		10.66	69.40	41	
19	10/13/1993	9/1/1994	Biopsy	13.9	13.90	69.12	11	early w/d SAE (<24 months)
23	11/16/1993	2/6/1997	Biopsy		13.80	69.38	39	
24	11/11/1993	11/10/1994	Biopsy		7.34	69.39	12	Unfavorable due to histology changes & ↑ALT
27	11/11/1993	3/7/1997	Biopsy		21.17	69.38	40	
28	11/16/1993	3/5/1997	Biopsy		17.20	69.38	40	
30	11/17/1993	11/26/1997	Biopsy		26.63	69.42	48	
33	2/3/1994	7/14/1994	Biopsy	15.7			5	w/d on 7/11/94; Aggranulocytosis
35	11/30/1993	3/13/1997	Biopsy		8.12	69.38	40	
36	1/12/1994	3/6/1997	Biopsy		13.17	69.38	38	
38	12/1/1993	3/7/1997	Biopsy		22.72	69.38	39	
39	3/10/1994	3/14/1997	Biopsy		11.59	69.38	36	
44	9/20/1995	6/12/1996	Biopsy		3.99	47.2	9	Unfavorable due to doubling of HIC
44	9/20/1995	6/19/1997	Biopsy		8.10	47.1	21	HIC quadrupled
45	9/20/1995	12/10/1996	Biopsy		8.60	69.38	15	
45	9/21/1995	3/14/1997	Biopsy		14.90	69.38	18	
59	1/13/1994	8/21/1996	Biopsy		17.29	69.38	31	
61	11/8/1993	6/29/1993	Biopsy	16.17	16.30	69.25	-5	last dose 4/26/94; SAE Cardiac Failure
63	4/13/1995	6/22/1997	Biopsy		4.20	64.1	25	Unfavorable due to ↑ALT
67	9/26/1995	3/27/1997	Biopsy		19.60	69.39	18	

No data were excluded based on whether or not the results were favorable or unfavourable to a study therapy. For 19 (subjects #5, 6, 11, 14, 17, 23, 27, 28, 30, 35, 36, 38, 39, 44, 45, 49, 59, 63, 67) of the 26 subjects listed in the table above, the LIC values and dates provided by the investigator show that the assessments were conducted 2-17.5 months (average 9 months) after trial termination. The sponsor does not have these values in the CRF or database. Nonetheless, the values provided in the table above show that for subjects # 6, 17, 39, 59 and 63, the new values are either lower than the last value included in the analysis database or still lower than the patient's baseline value, indicating that these values are not unfavourable to L1 (deferiprone).

One subject (subject # 4) was excluded because no baseline value was available within the 12 months prior to or 6 months after the start of study medication, as required in the study protocol.

In one subject (subject # 12), the value taken on the last day of study medication was not provided to the sponsor. This new value is lower than the last value included in the sponsor's analysis (6.5 vs .12.83), thus not unfavourable to deferiprone.

In another 2 subjects (subject # 24 and 44), the values were taken on the last day of study medication and they had not been provided to the sponsor. If the new value for subject # 24 had been provided to the sponsor, it would indicate a favourable response to deferiprone as it would be a decrease from the baseline result (9.4 to 7.34).

The reason for inclusion of subject # 61 in the table above was "SAE Cardiac Failure". A narrative for the patient's SAE has been provided to the Agency on [REDACTED] of the LA-01 Clinical Study Report.

The reasons for inclusion of subjects #19 and 33 in the table above were "early w/d SAE (<24 months)" and "agranulocytosis", respectively. Narratives for the adverse events that led to withdrawn of these 2 subjects from the study are provided on [REDACTED] of the LA-01 Clinical Study Report.

The reasons stated for inclusion of subjects #12 and 63 in the table above were "unfavourable due to ↑ALT results", while the reason for inclusion of subject # 24 was "unfavourable due to histology changes & ↑ALT". Increased serum ALT levels were not reported as an AE in any of these subjects. For subject # 12, on DCF# L604 (signed by Dr. Koren), the increased ALT at Month 12 (63 U/L) and ALT (177 U/L) at Month 14 were considered 'not clinically significant'. For subject # 63, the baseline ALT value of 304 U/L was higher than on treatment values. All ALT values were commented as 'not clinically significant' by investigator on chemistry CRF. For subject # 24, on DCF# L606 (signed by Dr. Koren), the increased ALT and AST from Months 2 to the end of study were considered 'not clinically significant'. Hepatomegaly and Jaundice were reported for subject # 24 on day 235 (0.64 years); however, both AEs were considered by the investigator (Dr. Olivieri; see DCFs L333 and L334) as "doubtfully" related to deferiprone. There are also hand-written notes by investigator indicating very poor compliance with deferiprone. Four months after onset of those AEs, the subject was withdrawn from the study due to "patient requested Desferal".

ApoPharma is unclear regarding the meaning of the statement "Included but with CRF error; no available source doc for PI's data" that is listed in the table above for inclusion of subject # 15.

- k) **Page 13; Paragraph 1: “In Dr. Olivieri’s analysis, all L1 Subjects appearing in the 24-Month Completer Analysis [REDACTED] experienced unfavourable outcomes (sustained efficacy without adverse events) by the end of treatment. Only the data line listings for Subjects 26 and 30 include the final end-of-treatment assessments.”**

Again, it appears that the Inspector has provided unauthorized information to the investigator, a matter to be addressed separate from this document.

ApoPharma has provided an objective assessment of the results of the study and is not privy to Dr. Olivieri’s analysis. No discussion of what constituted that analysis is provided and thus ApoPharma is not able to comment on this statement further.

- 1) Page 13; Paragraph 1: "Dr. Olivieri also disagree with the characterization of subject # 19 's adverse event as "neutropenia" and said this was more accurately "agranulocytosis". Her Adverse Event records are included as Exhibit 70."

It is unclear to ApoPharma what Adverse Event records were provided by Dr. Olivieri to the inspector, which are referred to as [REDACTED] as ApoPharma was not provided a copy of this exhibit. The Patient Listing of Discontinued Patients [REDACTED] referred to in the FDA inspection document, presents the verbatim adverse event term entered by the investigator on the end of study CRF page. In this case, as well as in the corresponding SAE form, the investigator reported this event as 'neutropenia' (see below).

**ADVERSE EVENT FORM**

**EACH ITEM INFORMATION** (to be provided for all serious and/or unexpected side effects, injury, toxicity or sensitivity reactions)

Patient ID/Initials: [REDACTED]		Age: [REDACTED]	Sex: [REDACTED]	Weight (kg): [REDACTED]	Height: [REDACTED]
Date of Onset (yy.mm.dd): [REDACTED]		Date reported: [REDACTED]			
Suspected reaction(s) (include a description of duration and frequency of - NEUTROPENIA (see paper attached) without clinical symptoms			Outcome of reaction to date <input type="radio"/> Alive with sequelae <input checked="" type="radio"/> Recovered <input type="radio"/> Still under treatment for reaction <input type="radio"/> Died (date)		
Check all that apply (if any of these criteria apply, this should be considered a Serious Adverse Event): <input type="radio"/> Life Threatening <input type="radio"/> Fatal <input type="radio"/> Permanently or severely disabling <input type="radio"/> Congenital Anomaly <input type="radio"/> Cancer <input type="radio"/> Overdose <input type="radio"/> Subject hospitalized or hospitalization prolonged					
In your opinion, how is this reaction associated with the suspect drug? (The opposite side of this form contains criteria which should be used in the causality assessment) <input type="radio"/> Definite <input type="radio"/> Probable <input checked="" type="radio"/> Possible <input type="radio"/> Conditional <input type="radio"/> Doubtful					
Describe the severity of the reaction (the opposite side of this form describes criteria which should be used in the severity assessment): <input checked="" type="radio"/> Mild <input type="radio"/> Moderate <input type="radio"/> Severe					
Test/Laboratory Data pertaining reaction - CBC + differential 5 day - marrow biopsy ( [REDACTED] ) - virology with CMV, EBV, influenza v, parvo			Was outpatient treated for reaction? <input type="radio"/> Yes <input checked="" type="radio"/> No		
			Was hospital treatment for reaction required? <input type="radio"/> Yes <input checked="" type="radio"/> No		
<b>SUSPECT DRUG INFORMATION</b>					
Suspect Drug Name: <i>Li</i>		Total Daily Dose: <i>2500mg/day</i>		Route of Administration: <i>p.o.</i>	
Indication for use: <i>chelation therapy</i>					
Therapy dates: From [REDACTED] To [REDACTED]					
Was treatment with drug reduced in dosage? <input type="radio"/> Yes <input type="radio"/> No    OR <input checked="" type="checkbox"/> Discontinued					
Did reaction abate after dosage reduction? <input type="radio"/> Yes <input type="radio"/> No					
Was drug reintroduced or dose increased? <input type="radio"/> Yes <input type="radio"/> No    / <i>not yet tried</i>					
Did reaction reappear after reintroduction or increase in drug? <input type="radio"/> Yes <input type="radio"/> No					
<b>RELEVANT/CONCOMITANT DRUGS AND MEDICAL PROBLEMS</b>					
Other Drug(s)	Total Daily Dose	Route	Dates of Administration From - To	Indications	
<i>PEGAZOLE</i>	<i>15 mg</i>	<i>p.o.</i>	[REDACTED]	<i>URTI</i>	
<i>CLAVULIN</i>	<i>750 mg</i>	<i>p.o.</i>	[REDACTED]	<i>URTI</i>	
<i>TYLENOL</i>	<i>1300 mg</i>	<i>p.o.</i>	[REDACTED]	<i>URTI</i>	
Other relevant medical history					
Sponsor Name and Address Rb Pharmaceuticals Inc. 104 Chancellor Matheson Road Winnipeg, Manitoba Canada R3T 2N2 Tel: (204) 989-6833/6830 Fax: (204) 269-7003		CLINICAL STUDY CODE (if applicable):  <i>19.</i>	INVESTIGATORS SIGNATURE: <i>Mat. Beakoutel</i> Print Name and Address of Investigator:		

Subsequently the event progressed to agranulocytosis and was therefore reported in the clinical study report as such. A copy of the narrative of this adverse event as described in

the LA-01 Clinical Study Report submitted to the Agency on 29 Jan 2009 is provided below.

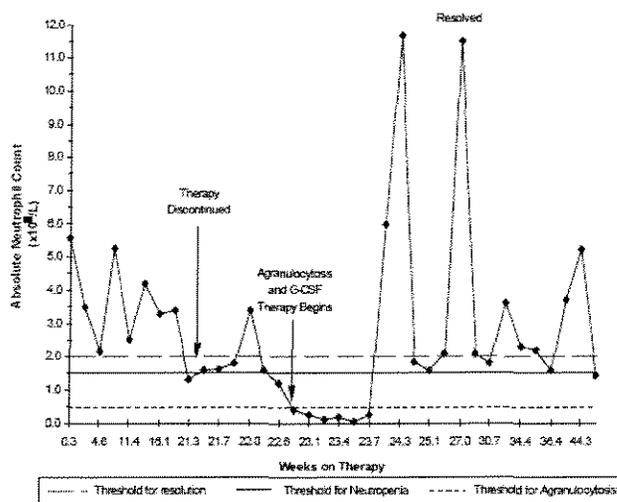
### Other Serious Adverse Events

Patient #19: One episode of agranulocytosis occurred in a 12 year old female patient (#19) treated with deferiprone for iron overload secondary to thalassemia major. She was on a regular transfusion schedule (every 4 weeks) with no other medical problems. She entered the clinical study and started deferiprone therapy on [REDACTED]. In [REDACTED] she acquired a prolonged (about 3 weeks) viral infection for which she received Pediazole (erythromycin ethylsuccinate and sulfisoxazole acetyl combination product), Clavulin (clavulanate potassium) and Tylenol (acetaminophen). On [REDACTED] a laboratory test for this patient revealed mild neutropenia with a neutrophil count of  $1.29 \times 10^9/L$  and on the basis of that count, deferiprone therapy was discontinued on [REDACTED]. At the time of discontinuation of deferiprone, there were no clinical symptoms associated with the neutropenia, and the results of the bone marrow aspiration and virology tests (EBV, CMV, influenza virus, parvovirus) were normal. On [REDACTED] the neutrophil count had dropped to  $0.4 \times 10^9/L$ , and a diagnosis of agranulocytosis was made. At that time, bone marrow aspiration showed decreased cellularity; granulopoiesis was markedly decreased and showed a virtual absence of forms beyond the promyelocytic stages. The patient was treated with G-CSF. Although after 5 days the patient's ANC remained above  $1.5 \times 10^9/L$ , the episode was considered resolved on [REDACTED] based on the criterion for resolution of two consecutive ANC greater than  $2.0 \times 10^9/L$ , at least three days apart.

ApoPharma Inc.  
Innovative Drug Division of Apotex Inc.

Ferriprox® (deferiprone)  
Study Report LA-01

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### Page 13: "Informed consent forms were observed..."

ApoPharma considers the statement inaccurate. The LA-01 Study Report notes omissions that some informed consents were obtained or signed after patient enrolment. There is no mention in the inspection report of the checking for such omissions in spite of these cited protocol violations in the LA-01 Study Report.

**Page 13; General Discussion with Management: the inspector confirmed the presence of informed consent forms, physician consults and other tests and assessments required by the protocol but was not able to review them for compliance with the protocol-specified timeframes for performance. Based on the data provided to the inspector, it appeared there was sufficient data to conclude that the subjects were eligible to participate and that the protocol-required tests and assessments were performed.**

Apparently, due to the lack of sufficient time and the unavailability of source documents for most of the study subjects, the inspector was unable to review in detail the protocol violations that were reported in the LA-01 Clinical Study Report. It is unclear, for example, that the inspection report makes no comment that the informed consent were reviewed, only that they existed. Examples of protocol violations cited in the Clinical Study Report and not addressed by the Inspector are provided below:

- Two subjects (patients #46 and #49, both aged 6 years had their informed consent form (ICF) signed and were randomized prior to IRB approval of modification # 8 which amended the inclusion criteria to allow patients as young as 6 years and 10 months.
- Patient #38 entered the trial and began treatment with deferiprone prior to signing the ICF (treatment was initiated on [REDACTED] but the consent was not signed until [REDACTED]).
- All baseline assessments were to be performed within 6 months preceding initiation of study therapy. On August 15, 1994, protocol modification # 5 allowed baseline assessment to be performed within 12 months of initiation of study therapy. Twelve patients (deferiprone-treated patients #4, #6, #17, and #24, and DFO-treated patients #1, #3, #8, #18, #21, #53, #56, and #62) were randomized prior to August 1994 using baseline liver biopsy values performed 13 to 16 months prior to study entry.
- Two patients were incorrectly stratified. Patient #64 on DFO entered the trial without a liver biopsy and was randomized based on the liver iron concentration obtained by SQUID. Patient #1, also on DFO, was stratified to the low liver iron stratum based on a SQUID of 2.96 mg Fe/g liver, dry weight even though a liver biopsy of 10.81 mg Fe/g liver, dry weight was available.
- During the trial the investigator at the Toronto sites failed to schedule a total of 65 (deferiprone 27, DFO 38) patients for either their annual, early termination, or study completion of the primary efficacy endpoint (LIC assessments) according to protocol. The end result was that some patients were assessed more frequently than others, not all patients were assessed within the expected time frame of their annual assessment date.
- Some of the LIC results recorded in the CRF could not be compared to the original source documents (SQUID reports at the MetroHealth Medical Centre in Cleveland, Ohio, where the assessments were performed) as the reports were not provided to the sponsor.

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