APPENDIX E:
Dr. M.N.G DUKE'S AUDIT OF TORONTO DEFERIPRONE TRIALS

Report of Dr M.N Dukes

AN ASSESSMENT OF ALLEGED PROTOCOL VIOLATIONS IN THE CONDUCT OF THE STUDY LA-01

In the matter of

DEFERIPRONE

AN ASSESMENT OF
ALLEGED PROTOCOL VIOLATIONS
IN THE CONDUCT'OF STUDY LA-0l

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EXECUTIVE SUMMARY

I have examined more than 3000 allegations made by Messrs Apotex with respect to supposed irregularities and deviations from protocol in the conduct of Study LA-01. Each allegation was checked against detai1e~ information regarding the 'patient to whose case the allegation referred.

The bulk of the allegations related to supposed failure to perform essential tests or investigations during the course of the study; more than half of them concerned haematological testing but they related to aspects of the study, including studies of liver function, iron metabolism and a range of clinical and laboratory tests. A small number of miscellaneous allegations concerned the supposed ineligibility of particular patients to participate or continue in the study

In summary, my findings were as follows:

- Well over half of the allegations (nearly 2000) relate to Apotex having failed to locate certain information, leading the firm to the false conclusion that this was lacking and therefore that particular tests had been omitted. For example, where a test was required a particular month, Apotex failed to determine whether it had been performed some days earlier or later and therefore failed to detect it. Handwritten records were in many cases overlooked. In virtually every single case I have succeeded in locating the relevant data and confirming the "missing" tests were both carried out and reported in the patient and trial records.

- Another substantial proportion of the 3000 allegations result from a misreading of the protocol by Apotex, leading the firm to conclude that certain tests were required where this was not in fact demanded by protocol. This error was most prominent with regard to haematological testing

- Apotex's own sudden termination of this study led to unforeseen complications with data since the protocol did not specify clearly how closing-out studies were to be handled under these extraordinary conditions. In the great majority of cases, even closing-out tests not demanded by protocol were performed.

- I conclude from my study that the number of deviations from protocol in study LA-01 was negligible and further that these were minor and of no possible significance to the outcome and interpretation of the trial

1. INTRODUCTORY REMARKS

1.1 Background

A fundamental argument raised by Apotex in its submissions to contest the application made to the European Court by Dr Olivieri is that the conduct of study LA-O1 was defective. In their argument, the protocol was violated on numerous points and it was therefore justifiable for the firm to set aside the findings. The alleged violations of the protocol are also advanced as proper grounds for Apotex to have terminated the study prematurely, as justification for its failure to request the Applicant to sign the trial reports, and as an element which rendered it unnecessary for the EMEA to undertake GCP inspection of the study. More genera1ly, Apotex argues (here in parallel with the Commission) that in view of these supposed defects of execution study LA-01 was not (and could not have been) a decisive basis for the positive decision taken b by the European authorities.

1.2. Scope-of the alleged violations

The essence of the allegations is that the protocol was not followed, notably as regards the performance of the numerous control investigations needed, both prior to enrolment of patients and during execution of the study. I note from earlier material that the number of violations which Apotex claims to have detected has progressively increased. In an internal memorandum of June 21st 1996 of which I have had sight; .6 violations were alleged with respect to hepatic iron concentration (HIC) and 16 regarding Serum ferritin (SF); in the Apotex Appendix 15.2.2. to the LA-01 report however the total number of alleged violations of all types has now risen to more than 3,000. My initial impression was that Apotex must have engaged in a hunt for-anything resembling a. formal deviation from protocol in order to arrive at this picture; my thorough examination of the study material does seem to confirm this impression, but much more significantly it reveals gross and overwhelming inaccuracies in the allegations made by Apotex.

1.3. Method of analysis

I examined in the first instance the study protocol for LA-01 in order to understand its requirements; in short, it may be considered to have been a sound and realistic protocol. All of the modifications made after it was originally drawn up were agreed and signed by the investigators and the sponsor; in most (but not all) cases the modifications were specifically motivated in writing; all appear reasonable.

In the *second* instance I considered the content of the Good Clinical Practice Guidelines which may be considered applicable to any such study.

In the *third* instance I considered all the allegations made by Apotex and compared each of these with the study materials and with-the aforementioned standards to determine whether there had been a violation of the protocol or not (and if so, whether it was of significance).

I would add that I have not gone back to all of the *original* patient record sheets as they exist in Canada nor have I conducted an on-site visit, though I am willing to do either if this is requested. The study results with individual patient data and photocopies of charts and clinical reports were made available to me in 13

volumes and these provided me with all the data needed for my study. Those 13 binders are divided by category of protocol violation (to correspond to the allegations as set out in Appendix 15.2.2), treatment group (deferiprone versus deferoxamine) and study subject; number for ease of reference. Personal identifiers were blocked out of all source documents, and study subjects were referred to by the number originally assigned to them for the purposes of the study.

1.4. The reality of clinical studies

In carrying out an assessment such as that required here, it is important to realize that in the conduct of any clinical investigation one is dealing with ordinary human subjects, biological measures, and the realities of everyday life. All are subject to a range of variation, in addition to which there are commonly practical constraints on the work which can render it impossible to act *exactly* according to the strict letter of the protocol. This is a given fact of clinical investigational life; it is quite different from the conduct of an experiment in physics or chemistry. These realities have to be taken into account in setting standards of good clinical practice, in designing protocols, and most important of all in assessing the conduct of the study and the outcomes which have been recorded. Where an extensive study has to be carried out involving large numbers of patients, collaborators and tests, there will be certain acts and omissions which are not in every miniscule respect ideal. One patient misses a bus and arrives after the laboratory is closed; another is briefly absent because of a school examination, a holiday or a concurrent illness; a liver biopsy may fail to obtain representative tissue; or a slip in the laboratory may invalidate a test. These things happen, and if each were to be a reason for rejecting an entire study virtually no clinical investigation would ever be accepted as valid. The fundamental question must be how serious and how numerous such events were when set against the totality of information. An ambitious clinical study with numerous measures will involve tens of thousands of steps; even a 1% 'incidence of minor deviation may therefore result in several hundred opportunities to question the validity of the study if one is positively seeking to discredit it.

In these matters I thus subscribe entirely to the view of Dr. Olivieri that in clinical investigations a certain number of protocol violations are inevitable and that some such deviation indeed occurred in the course of LA-01.

1.5. Significance of protocol deviations in study LA-01

There are two reasons to look most critically and cautiously at allegations of protocol deviations in this particular study.

The *first* is as set out in the above section: *entirely insignificant deviations from the norm must not be misrepresented as gross errors of execution.*

The *second* is at least as vital. At a given phase during the execution of this study, Dr Olivieri encountered data strongly suggesting that deferiprone was insufficiently effective. That evidence has been made known to the Commission and I will not repeat it here. Bearing in mind that the research-based European firm Ciba-Geigy had abandoned further development of the drug after pre-clinical evaluation (animal studies), (Berderkas et al, "Toxicity of Oral Chelator L1" Lancet 341: 1088-1089) one should have been extremely wary from the start, and the emergence of these conclusions was not at all surprising. *The strength of this*

evidence of an unafvourable harm/benefit ratio is such that, when set against it, the alleged deviations from protocol pale entirely into insignificance.

1.6. Presentation of analysis

I shall in the body of this report examine in turn the various areas of work in which deviations from protocol are alleged to have occurred. Under each heading I shall consider successively:

A. **The demands made by the protocol.** I shall also take into account here the modifications to the protocols which came into force at various times.

B. **The nature of the alleged deviations** (as set out in Apotex's appendix 15.2.2 to the LA-01 study report)

C. **Comments made by or on behalf of Dr Olivieri herself.** I use here primarily her Statement which is already known to the Commission and explanatory information which accompanied the source documents.

D. **Examination of the material:** I have concentrated here on the study documentation relating to those patients and situations instances in whom or in which failure is alleged to have occurred. I have examined all the relevant material, but in this report I shall for the sake of compactness use tabular overviews and in some cases randomly selected examples.

E. **The overall picture.** I discuss here the total picture as it emerges from the study record, including the data which I have not detailed in tables

F. **My conclusions**
In a closing section to the report I shall present my overall conclusion.

1.7. Qualifications of the author

I have in my Witness Statement of November 12th 1999 under "Relevant experience and training" provided an outline of my qualifications to provide advice in the matter of Deferiprone. I agreed to act as an expert in this matter primarily because of my long experience –initially in the pharmaceutical industry and thereafter with a national regulatory agency, the CPMP and the World Health Organization - in the organization, supervision and evaluation of clinical studies of drugs. This experience continues to grow with my active role in the establishment, review and further development and training of drug regulatory agencies in a wide range of countries; since January 2000 I have provided training and assistance to regulatory bodies in Mozambique, Australia, India, Laos and East Timor.

2. ANALYSIS

2.1. BASELINE SQUID OR BIOPSY

A. The demands made by the protocol

A *revised protocol* for LA-01 states that " ...liver biopsies and the other pre--trial assessments must be performed within the 12 months preceding the initiation of therapy in this study." (protocol revision signed by al .parties in July and August 1994) This represents a modification of the protocol prepared in May 1993 where reference was to a 6-month period; the change seems to me reasonable but the reasons for it are not given in the text of the protocol modification.

The various protocols make it entirely clear that while the non-invasive SQUID method for determining liver iron content is basic to the study, liver biopsies will generally also be performed (particularly since they are helpful in clinical and histological; assessment). Although both SQUID and biopsy are thus advised by the protocol, an agreed modification of February 8th 1994 noted that "...There *are a few patients that are eligible for enrolment in this study who cannot be assessed for liver iron content by the SQUID method. The reasons for this difficulty include past surgery and the weight of the patient. This subgroup of patients represents a population that would normally be found in clinical practice and it is felt that it is important to include clinical experience with these patients in this study.* This explains why one encounters among the results a very small number of patients in whom SQUID was not performed. This is entirely consistent with the protocol.

B. The nature of the alleged deviations (Appendix 25.2.2.1)

For reasons Apotex does not explain basing itself on the *original protocol* rather than the revised protocol which governed the study at the time of its termination, Apotex refers to 45 patients in whom a baseline SQUID or biopsy (to measure HIC's) was not conducted within 6 months prior to entry into the study. 22 of these entered the deferiprone group, the remaining 23 the deferoxamine group.

C. Comments made by or on behalf of Dr Olivieri herself

Like myself, Dr. Olivieri uses the 12-month requirement of the revised protocol that only in four patients were prior measurements not obtained within twelve months. In two of these HIC measurements were made within 12 months and 12 days prior to commencement. In a third case the measurement was made in 13'months. In a fourth case the measurement was obtained within 15 months of commencement.

D. Examination of the material

Looking at all instances in which the firm asserts that *either* of these studies were conducted *more .than* 12 *months* ahead of entry, I have examined the following cases and note my findings as regards the studies which I found:

Case 1:	(deferoxamine group)
SQUID:	16 months and 2 days prior to entry
Biopsy:	14 months and 14 days

Case 2:	(deferiprone group)
SQUID:	13 months and one day
Biopsy:	8 months and 15 days (i.e. COMPLIANT)

Case 3:	(deferoxamine group):
SQUID:	12 months and 12 days
Biopsy:	12 months and 27 days ahead.

Case 4:	(deferiprone group)
SQUID:	12 months and 5 days
Biopsy:	12 months and 12 days

Case 6:	(deferiprone group)
SQUID:	9 months and 26 days (i.e. COMPLIANT)
Biopsy:	12 months and 18 days

Case 8:	(deferoxamine group)
SQUID:	8 months (i.e. COMPLIANT)
Biopsy:	12 months and 15 days

Case 10:	(deferoxamine group)
SQUID:	12 months and 12 days
Biopsy:	12 months and 30 days

Case 17:	(deferiprone group)
SQUID:	Not available
Biopsy:	12 months and 27 days

Case 18:	(deferoxamine group)
SQUID:	12months and 27 days
Biopsy:	13 months and 7 days

Case 21	(deferoxamine group)
SQUID:	11 months* (i.e. COMPLIANT)

*The date entry for SQUID in the Apotex allegation is misprinted; I have not found the correct date in the patient summaries, but the 11-month period is not contested
Biposy:13 months and 14 days

Case 24:	(deferiprone group)
SQUID:	Not available
Biopsy:	12 months and 10 days

Case 53:	(deferoxamine group)
SQUID:	12 months and 30 days
Biopsy:	13 months and 8 days

Case 56:	(deferoxamine group)
SQUID:	11 months and 29 days (i.e. COMPLIANT)
Biopsy:	13 months and 11 days

Case 62:	(deferoxamine group)
SQUID:	12 montJ1s and 23 days
Biopsy:	15 months and 27 days

**Following examination the patient requested delay in the date of entry into the study, a request which was specifically agreed to by the Apotex monitor.*

E. The overall picture

1. From the above citations from the protocol and its modification, I conclude that the non-invasive SQUID method and liver biopsy were both recommended and regarded as equivalent, though in some patients one or the other might not be feasible. I feel it is therefore reasonable to conclude that, provided. one of these two were performed within the period, demanded by the protocol, it is not serious if the other fell somewhat outside this period.

2. I further take as my starting point the fact that, at the time in question, the requirement was that the measurements be taken 12 months before commencement and not 6 months as originally decreed.

3. I next have to consider how one should interpret the "12 month" requirement. Shall a period of 12 months and some days be regarded as a contravention? Looking through the entire series and seeing how many of the prior assessments were indeed made approximately twelve months ahead I conclude that a serious effort was made to respect the twelve-month deadline, and that a little variation in either direction (10-13 months), dictated by the practical realities of getting patients to attend precisely on schedule, cannot reasonably be termed a "violation".

4. If I apply these standards to the above analysis I can identify only Case Nr 1, where either test was performed within 14 months, as a marginal violation. In the remaining cases at least one of the two tests were carried out "12 months plus X days" before entry.

5. Even if one were to regard all the above 14 cases as "violations", which in my view would be absurd, one would have to note that they came from both the deferiprone and the deferoxamine groups (9 vs. 6, which is not a significant difference), and that any resulting distortion of the trial would apply to either group.

6. Nor can I, after looking at the data in the individual patients, identify any element in the results of later tests or in the outcome which could raise doubts as regards the validity of the pretrial measurement. In patient Nr. 1, for example, where the initial SQUID test was performed 16 months in advance, on October 8th 1992, repeated later SQUID measurements of mg/Fe/ gm taken in 1993 (well before entry baseline was determined in 1994) are available from the record; they show such marked variations in the course of a few months that it is hardly likely that a single SQUID take within the 12 month period would have added more relevant information

F. My conclusions

The Apotex allegations of protocol violation as regards baseline measurements cannot be taken seriously. They are based on Apotex having had recourse to an earlier protocol which was replaced in good time. And it is notable that the Apotex monitor agreed to that revision of the protocol. In the overwhelming bulk of cases the measurements *were* reasonably in accordance with the revised protocol in force at the time they were made and whatever marginal deviations may be pointed to if one adopts an excessively formalistic approach they could have had no practical consequences whatsoever: Although my analysis of figures and dates differs in minor-detail from that made by Dr. Olivieri, since I have adopted a different approach, I agree entirely with her that one cannot speak here of <u>any</u> significant protocol violation..

2.2. INCOMPLETE SQUID OR BIOPSY AFTER. BASELINE

A. The demands made by the protocol

The protocol for LA-01 requires studies of hepatic iron concentration.(HIC) at entry baseline, at 12 months and at 24 months. Apotex has acknowledged in section 8.4.2. of its Clinical Study Report L1-01 as submitted to the Commission that a scatter of these dates by up to 6 months in either direction is permissible.

In cases of elective withdrawal, a final SQUID or biopsy is not mandatory but will be performed if possible (see Section 6.0 para. 6 of the original protocol, page 16). This does not appear to have been modified in any protocol. I note that s modification to the protocol signed by all parties (including Apotex) in July and arid August 1994 made express reference to 'the difficulty of doing a liver biopsy or SQUID more than once per year per patient unless clinically indicated. Moreover, Apotex's premature termination of the trial cannot be characterised as "elective withdrawal". Similarly "study termination" is specifically defined in Section 5.4 para. 13 of the protocol, or withdrawal; it does not contemplate termination of the study by Apotex.

The motivation behind the termination was the alleged protocol violations on the part of Dr . Olivieri. There is no express provision in the protocol dealing with this scenario and hence there can be no violation of a protocol which does not provide for any procedure to be complied with. Indeed, in principle how could Dr Olivieri conduct the assessments when, by virtue of the premature termination, she was prohibited by Apotex from 'conducting these assessments? Alternatively, the situation arising could arguably he said to fall within the second paragraph of Section 7 of the protocol which provides that in the event of termination for safety reasons the investigator is required <u>only</u> to deliver up the drug and the existing documents. The final paragraph of Section 7 of the protocol covers the case where termination arises for non-safety

reasons. In such a case the investigator is to deliver up the drug and the documents to the sponsor and "carry out the necessary assessments for termination of study." In the present case the evidence given by Apotex (see para 37 of the statement of Dr Spino) is that on 24 May 1996 A,potex both terminated the trials for LA-01 and LA-03 and the consultancy agreement with Dr Olivieri for LA-02. Dr. Olivieri, however, was of the view that she should conduct further assessments and in order to. Achieve this she sought exceptional funding through the Emergency Drug Release procedures instituted under the Food arid Drugs Act of Canada (Application paragraph 4.18). In other words, Dr Olivieri endeavoured to conduct the very tests she is now alleged to be guilty of failing to carry out, even though she had to do this without financial support from Apotex. From the analysis that I set out below she succeeded in her task. There was no protocol violation.

B. The nature' of the alleged deviations

In its appendix 15.2.2.2, Apotex maintains that there was failure to perform these studies on 6 occasions, 38 of these relating to the deferoxamine group and 27 to the deferiprone patients. It may be helpful to relate these figures to those for the number of patients in the trial: 75 patients were randomized for entry but only 71 received the therapy to which they were randomized. Assuming that all continued the trial sufficiently long, there would therefore be 3x71=213 measurements of HIC to perform; if both SQUID and biopsy are recommended this would represent a total of. 416 tests. Apotex thus asserting that a substantial proportion of the necessary tests were omitted.

C' Comments made by or on behalf of Dr Olivieri.herself

To paraphrase Dr Olivieri's reply she states essentially that in 24 of the 65 alleged instances of failure the measurements were indeed performed (i.e. the allegations are baseless). while in other instances certain later assessments were not feasible because the patient died or withdrew (or the study was terminated by Apotex itself).

D. Examination of the-material

1. I have traced and examined all the 65 instances where it is alleged by Apotex there was improper failure to conduct these follow-up tests. The analysis is somewhat complex since one is dealing in some cases with incorrectness of the allegations and in others with circumstances (notably death or withdrawal) rendering the test impossible.

2. From Apotex's own overview of its allegations it is clear that no less than 44 of the alleged instances refer to supposed failure to perform certain tests in patients who were involved in what Apotex calls "early termination".

- Deferoxamine group: cases 1, 9, 10, 16, 18, 20, 21, 22, 25, 31, 34, 37, 40, 43, 46, 47, 48, 50, 51, 53, 57, 62, 64, 65, 68 (25 of 38 alleged cases of failure)
- Deferiprone group: cases 2, 6, 12, 17, 24, 27, 29, 30, 35, 39, 44, 45, 59, 61, 63, 66, 67 (19 of 27 alleged cases)

However it is clear from the patient summaries that in 13 of these instances the termination of the study was not truly "early", in that 24'months of study had been completed and that the Study was indeed carried out according to protocol. In 8 instances on deferiprone (patients 12, 14, 15, 23, 28, 38, 59, 63) and 13 on deferoxamine (patients 3, 7, 8, 9, 22, 31, 34, 42, 55, 56, 60) it seems clear that Apotex's own. termination of the trial complicated the issue.

3. In this confused situation I can best illustrate what happened by presenting individual cases, confining myself for this purpose to the 19 cases cited by Apotex as supposed failure to test HIC in the deferiprone group in connection with "early termination". My personal hand written notes on the patients listed by Apotex as representing failure to test at 24 months, and on cases in the deferoxamine group give almost exactly the same picture:

Case 2:	Withdrawn after less than 3 months because of neutron[enia, hence the 12 and 24 month tests demanded by Apotex are obviously lacking.
Case [ ]	Cloes-out tests on Withdrawal were not considered to be clinically justified, and with this very early withdrawal they would have been meaningless.
Case 6:	Apotex speaks of lack of an "early termination" study but the patient papers show that studies were performed at -10, + 13 and +27 months; so the allegation' is incorrect.
Case 12	Despite abrupt termination some 30 months after enrollment, SQUID or biopsy were performed four times, including both pre-study and withdrawal; so allegations of failure are incorrect
Case 17:'	Termination was not until the 28th month,and HIC was performed at -13 +9 and + 25 months according to protocol. So the allegation is incorrect..
Case 24	Here HIC tests were carried out at -6, -5 and + 12 months, and the patient withdrew a month later. The test at -5 months can be considered as base1ine measurement (it .... was 'within the prescribed period) so there was no deviation from protocol. So the allegation is incorrect.
Case 27:	HIC tests were performed at –10, -9, +12 and +-26 months with termination at 29 months. The –9 months measurement was valid for establishment of the baseline, and the series as a whole provides a clear picture of the case. No deviation from protocol. So the allegation is incorrect.
Case 29	HIC tests .at -10 and -8 months. No further baseline measurement thereafter and no "close out" measurement on withdrawal at five months of treatment, but in view of the brief period .of treatment these would have contributed nothing.' So the, allegation is incorrect.
Case 30:	HIC studies at -9 (two tests), + 14 and + 26. No later baseline study was not done, but it was not required. Termination at month 31. So the allegation is incorrect. .
Case 35:	HIC studies at -8, -6, + 12, + 16 and + 31, the last following termination of the study at +29. Fully satisfactory. So the allegation is incorrect.
Case 39:	HIC studies at -12, -10, + 8, + 12 and + 24 (prior to termination of study)precisely according to protocol. So the allegation is incorrect.
Case 34:	HIC studies at -2 and +9, the latter after abrupt termination of the study. Protocol was followed. So the allegation is incorrect
Case 45:	C tests at -1,0 and 15 months according to protocol. So the allegation is incorrect

Case 49	HIC tests at -3 and +9 months, the latter after Apotex terminated the entire study. So the allegation is incorrect.
Case 59	HIC tests at -10,-8 + 10 and +31; the final test was thus later than it should have been, but it followed acute termination of the Study at + 28. So the allegation is incorrect.
Case 61	HIC tests at -5 and + 6 .months, according to protocol. Patient died at + 7 months and I note that post-mortem liver biopsy was refused, so allegation that a later study missing is nonsensical. So the allegation is incorrect.
Case 63	HIC tests at -3, -3 and + 12, the latter at the moment when Apotex terminated the Study. Fully satisfactory. So the allegation is incorrect.
Case 66	HIC tests at –2 and + 9 months according to protocol with termination of the Study by Apotex at the latter time. So the allegation is incorrect.
Case 67	HIC tests at -3, -2 and +9 ,months as required, with termination of the study at +8 months. Satisfactory I every way. So the allegation is incorrect

E. The overall picture

Examining the above group of 19 patients, and having found precisely the same picture in the other ., .. patients (on deferiprone or deferoxamine) who are the subject of Apotex's allegation of extensive protocol violation in this regard I can only express astonishment at the allegations. Quite simply 'there was virtually no failure. Sometimes SQUID was used, sometimes biopsy, often both. In a very occasional case a test was performed more than 6 months away from the date when it was due; in a few other cases, final tests on patients withdrawing very early from the study ((or dying) were omitted because they were pointless or were refused. Even where long-term patients were involved in the sudden termination of the study by Apotex final studies were as a role performed.

F. My conclusions

Quite simply: Apotex's allegations that there was failure to perform proper follow-up HIC studies are baseless. In the great bulk of cases the tests were performed and reported in the records within the prescribed time-frame.

2.3. COMPLETION OF SERUM. FERRITIN (SF) ASSESSMENTS

A. The demands made by the protocol

The protocol for LA-0I required that serum ferritin assessments be carried out at entry (baseline), then quarterly until month 24 but not at study termination._Section 6:0.para. 6 requires that the assessments normally done 2 years after therapy be done "if possible" but again (as noted with respect to SQUID or biopsy, after baseline)_this requirement is limited to cases of elective discontinuation of therapy. It does not apply to Apotex's premature termination of the study. The same is true for haematology, UIE, MRI compliance virology, vital signs and physical examination assessments. In this respect I refer the reader back to my considerations wider 2.2. (A)regarding the circumstances in which LA-01 was terminated by Apotex.

B. The nature of the alleged deviations

Here Apotex alleges that there were 131 protocol violations, an average of almost two per patient.

C. Comments made by or on behalf of Dr Olivieri herself

Dr Olivieri has commented that in fact, of the 131 instances cited, 92 were occasions on which SF was indeed determined; 5 relate to patients who died or withdrew early, 2 to instances related to Apotex's termination of the study. In her view there were at most 33 actual violations, and almost all of these were purely formal. She stresses the limited usefulness of SF as a measure of body iron burden.

D. Examination of the material

On examining the material I find that the true picture is extremely similar in the deferiprone and deferoxamine groups. For the sake of compactness I shall therefore limit this account to the deferiprone cases. I am listing the patient numbers, the points in the study at which a test is alleged to have been omitted and my own findings from the patient summaries with respect to these times.

ET = Test at early termination

Patient	Alleged omission at (months)	Test identified at (months)
6	9, 21, ET	8, 22
11	9, 15	9, 16
12	3, 9, 15, 27	3, 8, 14, 34
14	ET	(ET AT 7)
17	9, 18, 21	9, 17, 22
19	9	(WITHDREW EARLIER)
24	9	10
26	3, 9, ET	3 11
27	3, 6, 18, 21	3, 6, 18, 21
28	3	27
29	3	3
30	3, 9	4, 9
33	3, 6, 9, ET	ET WITHDREW AT 2
35	3, 15, 21, 27, "29"(?), ET	2, 15, – ,26
36	3, 12, 15	3, – ,15
38	3, 9, ET	2, 8, 11
39	3, 9, 15	3, 8, 15
44	ET	ET
45	9, ET	TERMINATED AT 8
49	9	TERMINATED AT 8
59	6, 27	6, 25
61	ET	DIED
63	ET	-

E. The overall picture

The Apotex allegations regarding the failure to perform numerous serum ferritin tests are almost entirely baseless. I can only think that the table of missing data was incompetently or carelessly drawn up. In most of the cases cited the "missing" test was performed a month earlier or a month later than planned, which could not in any way be regarded as improper but led the compiler of the allegation to believe that the test had not been performed. Assertions that "early termination "tests for SF are missing fail to note that they are not required by protocol; some were nevertheless performed.

The demand for a test at month 29 in patient 35 is not backed by protocol.

My notes on the corresponding series of deferoxamine patients show precisely the same picture.

In the whole deferiprone series I can only identify two missing tests.

F. My conclusions

The allegations of omissions regarding SF are almost entirely baseless; the author of the allegations simply did not examine the patient records properly.

2.4. ALLEGATIONS RELATING TO DEFECTIVE HAEMATOLOGICAL TESTING

The need for proper haematological testing in this type of study and patient is evident, even if it is not a primary endpoint for the investigation, but Apotex claims attention for no less than 1535 supposed violations in this field.

A. The demands made by the protocol

According to the protocol (and its fifth modification) a series of pre-trial haematological tests, using numerous measures are required. The protocol appears to require these studies only during the 12 months prior to the study and their number and frequency is not clearly specified but it appears to be monthly. Once the study has started, the deferoxamine group are to have CBC and white cell differential tested every two weeks, because of the drug's known haematological effects, while the patients taking deferoxamine are to be tested only monthly.

The protocol does not demand haematological studies on early termination.

B. The nature of the alleged deviations

Apotex's appendix 15.2.2 to the study report is very long but unclear, dealing almost exclusively with what it terms "pre-month" assessments. If I understand this correctly it means that only one record has been found in a. particular month, whereas two were alleged to be required. This explanation is suggested by a. note provided by Apotex in 15.22. This could be a fair requirement for deferiprone where the blood parameters have to be tested twice monthly, but one cannot remotely understand it for deferoxamine, unless Apotex is under a. misapprehension that twice monthly testing was also necessary in this group. This could explain why only 455 "deviations" are alleged to have been found for deferiprone but 1080 for deferoxamine. The number of alleged violations is in truth on any view grossly exaggerated because of a misreading of the protocol.

C. Comments made by or on behalf of Dr Olivieri herself

Dr. Olivieri appears to have the same difficulty as I do myself in understanding the Apotex allegations in this area.

D. Examination of the material

Because of the above problem, I will examine separately the deferiprone and the deferoxamine

455 violations are alleged in the deferiprone group and they relate to 29 patients, in many of whom massive numbers of missing tests are cited.

Because of the volume of the material I will examine a group of patients in the deferiprone series and compare the allegations with what I find in the summaries and patient records., Before doing so it is informative and illustrative to examine in detail the position of a single patient whose identity I !selected through "random" process. This is "Patient 4". This is a typical case where it is alleged that some protocol violations occurred

Patient 4:	Eight "pre-month" examinations of the haematology are stated to be missing, namely those for months 3, 4, 20, 23, 25, 26, 27, and 28. What I find in the records is:	
	Month 3: (2/94)	Although the patient was seen on both February 2nd and 16th, I find haematologial records only for the 16th.
	Month 4: (3/94)	The allegation is incorrect since I find haematological data both for March 16th and 30th.

	Month 20: (7/95).	I indeed find only one record this month, namely that for July 27th
	Month 23: (10/95)	Again I find a record only for October 25th.
	Month 25: (12/95)	The only haematological record is for December 18th.
	Month 26: *(11~).*	There is a record for January 3rd (which. is only two weeks after the December 18 record) .but there is nothing more until February.
	Month 27: (2/96)	Haematological record only for February 7th.
	Month 28: (3/96)	Record only for March 11th.

Looking at this patient Nr. 4 right throughout his/her treatment what I see is that for long periods twice monthly haematology was carried out according to protocol, but that there were some gaps around Christmas /New Year and in the middle of the summer holiday, which is not unusual.

In order to avoid the risk that it be suggested my selection was targeted I also examined a series of patients listed *consecutively* by Apotex as having inadequate haematology control.

Patient 11:	I can confirm that in 1995 there was only one haematological study monthly in the months of May,June, July and October, but there were twice-weekly studies at other times during that year
Patient 12:	Between months 2 and 30, twelve haematological records are stated to be missing. The handwritten records are a .little difficult to read, but during this period of 28. months (December 1993 to April 1996) I find tabulated and detailed records of 60 separate haematological studies, a little irregular but averaging just over one per fortnight.
Patient 13:.,	Only one test a month during November and December 93 'but fortnightly studies at all other times
Patient 14:	Apotex is right in stating that there was only one study in month 28 (April 1996) but this is due to slight irregularity; haematology was performed 8 times between January and April, an average of twice a month Apotex may also have been misled by reading only the computerized data sheet from the Hospital; the handwritten record is more difficult to. read but the additional studies are there.
Patient 15:	Apotex alleges that a single pre-month study was missing (in January 1996) but in fact the records are present for January 19th and 23rd - surprisingly close but there were indeed two studies that month. Apotex is also wrong in pointing to the absence of an early termination study of the haematology - none was demanded by the protocol but in fact two were performed at this time.'
Patient 17;	Apotex finds only monthly haematology during months 11,12, 13 and 17 (between November and May 1994/5) but in, fact ten separate haematological investigations were carried out during that 7 month period - about one every three weeks despite the usual irregularity around Christmas and New Year.
Patient 19:	Apotex points to only a single monthly haematology during months 2, 4 and 10 (12/93, 2/94 and 8/94). In fact I find three haematological records for December (8th, 9th and 30th) and two for February (1st and 23rd.). The requirement had disappeared by month 10 since the patient stopped taking the drug during month 5 (March 1994) because of toxicity; Apotex must have overlooked this. .
Patient 24:	Apotex points to a low (monthly) incidence of haematological studies during the period May-September 1994;there was certainly some irregularity during the summer but in the

	long term there was a higher frequency, e.g. 10 hematological studies were performed in the six months from January to June of that year.

I believe these cases are amply sufficient to illustrate the picture which I find throughout this section of the file.

E. The overall picture

The conclusion with respect to haematology is not dissimilar to that in other fields, but there additional errors in Apotex's massive list of allegations. The most fundamental here is that they overlook the fact that the patients in the deferoxamine group did not need to have their haematology tested twice monthly. Once 'again testing is demanded for months in respect of patients who had to examine carefully both the handwritten haematological records and set them alongside. the computerized record, and. by failing to consider the total frequency of haematological monitoring over a period rather than picking on months which only one study was done Apotex presents a thoroughly inaccurate and misleading picture of what. happened.

F. My conclusions

In general the haematological studies were carried out strictly according to protocol with only a little irregularity in some very few cases, probably due to seasonal events.

OTHER AREAS IN WHICH FAUTS ARE ALLEGED TO HAVE OCCURRED

The four technical areas of testing dealt with in section 2 above comprise the crucial part of the allegations raised by Apotex regarding deficiencies in the conduct of study LA-01. I will deal more briefly below with the remaining areas, but I find that in these areas also the allegations of failure are simply unsubstantiated.

3.1 Allegations regarding Urinary Iron determinations

Apotex alleges in its appendix 15.2.2.2 that no less than 372 measurements of urinary iron excretion are missing from the study – 164 in the deferiprone group and 208 in the deferoxamine patients. What the protocol demands (apart from the baseline) is measurements every three months; it makes no mention of requirements on termination.

The picture which emerges on a careful comparison of the patient laboratory tables is very much the same as we saw with respect to serum ferritin; the author of the allegations has failed to look assiduously enough at the records and has therefore overlooked a great deal, especially where tests have been performed just a little earlier or a little later than set by the programme. He/she has also overlooked the fact that UI determination is not required on early termination, and has alleged absence of tests for periods when patients had already withdrawn from the study or the study has been terminated. To save burdening the Court with my full notes, I have used a random numbers programme to select ten deferiprone patients, and all prove to illustrate these points well".

Patient Nr	Alleged tests missing (Months)	Tests found at (months)
4	6,9, 24, 27, ET	7, 10, 23, 27
11	3, 6, 9, 12, 21	1, 5, 7, 11, 12, 21
19	6, 9, ET	- (withdrew at + 5)
33	3, 6, 9, ET	2 (withdrew at +2)
39	3, 6, 9, 15, 24	3, 6, 10, 15, 23
44	3, 6, 9, ET	4, 6, (Term as + 8)
45	3, 6, 9, ET	3, 7, (term at +8)
61	3	- (withdrew < 6m)
63	3, 9, 12, 15, 3t	3, 8, 11 (term 13m)
67	6	

Conclusion: The allegations of protocol violations regarding measurements of urinary iron are inaccurate and baseless. Again the write has failed to look for tests a month earlier or later than the prescribed dates, and has overlooked the cases in which there was early withdrawal.

3.2 Allegations regarding incomplete assessment of compliance

These allegations are extraordinarily extensive, bearing on almost all the patients in the study, and touching on 546 supposed violations. Since deferiprone is an oral product and deferoxamine an injectable, the means used o check compliance were different for the two preparations. There were also special routines

for dealing with out-of-town subjects. The protocol did not require a compliance check at the time of early termination.

I have in this case again, for the sake of compactness, provided from my notes a selection of the patient material, once more using a random numbers programme, applied to patients in the deferiprone group.

Patient Nr	Compliance allegedly "lacking" at (months)	Compliance tests actually Identified at (months)
2	1, 2, 3, 4, 5, ET	1, 2, then patient withdrawn (+3)
6	1, 2, 4, 9, 10, ET	1, 2, 4, 9, 10
13	1, 2, 4, 6, 7, ET	2, 2, 5, 7,7,
23	1, 2, 8, 11, 14, ET	1, 2, 8, 11, 14, ET
27	1, 3, 10, ET	1, 3, 10
29	1, 2, 4, ET	1, then withdrawn
30	1, 2, 8, 9, 10, 13	1, 2, 8, 9, 10, 30
44	ET	ET
59	1, 3, 6, 7, 11, 18, 27, ET	1, 3, 6,-, -, 18, 28
61	1, 2,	1, 2

Here there were very occasional omissions, or some monthly records have been lost. Across the board however; it is impressive to see how complete the compliance records are. Patients were questioned, residual tablets counted, the Standard MEME calendar plotting system employed and patient diaries regularly examined. Very commonly more than one method is reported upon in each month.

Once more, however, it is disappointing to see how wildly inaccurate the Apotex allegations are, since almost all the "missing" compliance tests are in fact to be found in the patient records and summaries, while even those "early termination" checks on compliance which are not obligatory in the protocol often prove actually to have been performed. Checking of the remaining patients and those in the dferoxamine group shows the same picture.

3.3 Allegations concerning deficient virology testing

Virology testing was another supplementary measure, in this study, and it is the subject of 54 allegations of protocol violations, 23 of them in the deferiprone group, all on the subject of failure to perform viral antibody tests at the prescribed times. Baseline and six-monthly testing was to be carried out; no assessments were required for early termination, but no less than 13 of the 23 allegations regarding the deferiprone cases relate to this non-obligatory step. To consider the remaining 10 allegations (concerning 8 patients) in the deferiprone group:

Patient	Test :"missing" At month:	Tests identified At month:
14	24	24:HIV, HbdAb,HbdsAg
15	24	23:HIB,HbsAb,HbsAg,HCAb
26	30	None, terminated earlier
27	16, 18	6:HbsAb,HbsAg,HCAb 18:HIV,HbsAb,HbsAg,HCAb

28	24	26:HIV,HbsAb,HbsAg,HCAb 27:HIV,HbsAb,HbsAg,HCAbg
33	6	None, terminated earlier
39	6, 24	7,HIV,HbsAb,HbsAg,HCAb 24:HIV,HbsAb,HbsAg,HCAb
63	Baseline	Full studies at –7, -6, -3 and +5

It is clear from this representative series that full virus studies were indeed carried out regularly, in contract to what Apotex alleges. Apotex overlooks not only the fact that ET studies were not required by protocol. It also overlooks or ignores the fact that a fair proportion of the studies alleged to be missing relate to times at which the patients had been withdrawn from the study or occurred at a point in time after the study had been terminated.

3.4. Allegations re failure to perform physical examination

And

3.5. Allegations re failure to check vital signs

Again one is dealing with a supplementary measure, not with an essential endpoint In the study. Nevertheless Apotex alleges that at 152 points there were deficiencies in the conduct of the study.

The protocol calls for physical examination to be carried out monthly (quite apart from pre-trial examination). The content of the physical examination is not specified in detail.

An associated issue is that of vital signs (pulse, blood pressure and body temperature) which although they are usually considered part of a general physical examination, are dealt with as a separate issue in this study. Apotex claims that 166 deficiencies could be identified with respect to the checking of vital signs, 73 of them I the deferiprone group and 93 in the deferoxamine patients.

Review of the relevant patient files shows that in fact, in the great majority of cases, a clinical sheet was filled in monthly though it does not always specify precisely what was examined, and in an occasional instance a haemological sheet substitutes for it; in a few cases the best account of what was done is in a referral letter. The "vital signs" sometimes form part of the clinical record, whereas in other cases one finds them on a separate chart. Should the Court require or wish to see my patient-by-patient notes I will gladly produce them.

A typical (randomly selected) is Nr. 12 in the deferiprone group. According to Apotex the vital signs assessment was not completed at months 2, 7, 9, 11, 13, 15, 19, 20, 23, 25, 27, 29 and 23 (33?). On examining his/her records I find, from month to month:

Month 2	(12/93)	Records missing from file
Month 7	(5/94)	Vital signs chart completed
Month 9	(7/94)	Idem
Month 11	(9/94)	Idem (for 31/8 and 3/10)
Month 13	(11/94)	Idem

Month 15	(1/95)	Idem
Month 18	(4/95)	Idem
Month 19	(5/85)	Idem
Month 20	(6/95)	Idem
Month 22	(8/95)	Idem
Month 23	(9/95)	Idem
Month 25	(11/95)	Idem
Month 27	(01/96)	Idem
Month 29	(01/96)	idem

This example, which could be continued for many pages more with others, once more shows that in compiling its list of alleged violations Apotex has been less careful. Of the 14 "missing" sets of data, 12 are present in perfect form in this patient's records. A further one (for September 1994) is adequately replaced by sheets for August 31st and October 3rd. The only sheet which I do not find is that for March 2. Once more: this case is entirely typical of the entire section dealing with physical examination and vital signs.

My overall conclusion is there were no serious or material defects in the physical supervision of the patients, but from the very brief handwritten notes it is not clear what was done. This is a typical problem of most clinical trials: the general physical data are recorded in handwritten form, sometimes in a special manner prescribed by the hospital concerned, and is not at all easy to check the completeness of the examination. As might have been expected in such patients and such a trial, far greater emphasis was laid on the specific tests and examinations relevant to the progress of the disease and the trial, as considered I other sections of this report.

3.6. Allegations regarding inadequate MRI assessment

Allegations regarding failure to complete MRI assessment (magnetic resonance studies of the liver, heart and pituitary) forma relatively small part of appendix 15.2.2.2. They relate to 85 check points (39 involving 26 patients in the deferiprone group and 46 involving 31 patients in the deferoxamine group)

The protocol requires initial assessment either within the 12 months preceding entry or in the six months following. Thereafter MRI was to be preformed on the three organs at annual intervals and again on termination (completion of protocol or withdrawal). I refer the reader once more back to my discussion under section 2.2 (A) of the protocol requirements in the event of premature termination.

MRI is not without risk, and as a rule one will not wish to perform it in any patients without pressing reason more than once a year. In many cases of thalassemia major it will be performed annually and it would be unwise to perform a second MRI in the course of the year merely in order to fulfil a protocol obligation. Once again, a modification to the protocol signed by all parties in July and August 1994 made express reference to the difficulty of doing an MRI more than once per year per patient unless clinically indicated.

The allegations made by Apotex are generic, i.e., the simply name the patient and the time at which (according to the firm) MRI was negligently omitted, without stating whether this relates to the (joint) examination of liver/heart or examination of the pituitary.

If I take 26 patients in the deferiprone group, and go back to their original MRI reports I find the following

picture (that emerging in the deferoxamine group is virtually identical):

Patient	Alleged omissions (month)	MRI found by myself (month) HLP = Heart, Lung pituitary
4	ET	MRI(HLP) 3/96 (2m pre-ET)
5	ET	(HLP) 9/95 (8m pre-ET)
6	12 ET	15 (HLP). Repeat HLP 13d pre-ET
11	12	12(HLP) 11/94
12	24 ET	Out of town: record incomplete?
14	12 ET	11(HLP) 4/95 ET(HLP)6/96
15	12	10(HLP) (11/94)
17	12 ET	14(P)2/95 15(HL)3/95; ET(HLP)11/96
19	ET	-; withdrawn within 6m (toxic)
23	12 ET	17(HLP)4/95 ET(HLP) 9/96
24	ET	-; withdrawn within 12 m
26	ET	HLP 12/95 (5m pre-ET)
27	24 ET	26(P)1/96; ET(HL)3m post-ET
28	12 ET	20(HLP)7/95 ET(HLP)6m post-ET
29	ET	HLHL6m pre-ET;(P) 4m post-ET
30	12	15:MRI(P) 2/95 18⊗CL)5/95
35	24ET	Out of town; records incomplete
36	12 ET	19(HLP)8/95 EP(HLP)3m post-EP
38	12	15(HLP)3/95
39	12 ET	17(HLP)8/95 EP)HLP) 3m post-EP
44	ET	-; record incomplete?
45	ET	-; record incomplete?
49	BASE ET	Base HLP at 2m(11/95) No ET MRI
59	ET	P at 24m was only 4m before ET
61	ET	Patient died, hence no ET test
63	ET	-; record incomplete?
66	ET	HLP at 2m, 8m before ET
67	BASE	-; record incomplete?

In 5 of the 26 patients I have not until now been able to find any or all the MRI data which may exist. This does not mean the data does not exist or that the test was not carried out but only that it is, so far, inaccessible especially in the case of out of two patients. In the remaining 21 patients I find that – bearing in mind that we are speaking of an approximately annual study of the need to attune the timing to a pre-existing timetable of regular MRI's, and of the importance of not repeating MRI's at too short an interval – adherence of protocol was very reasonable, and as a rule all three organs were examined.

As in other matters, the author of the Apotex allegations has failed yet again to look at the records sufficiently carefully. The above table shows that of the 39 allegations of non-performance, 13 related to tests which actually hade been carried (sometimes a little earlier or later than strict adherence to the calendar would demand – which is in this case not a problem). 23 of the others concern the supposed absence of MRI tests on early termination; in most of these cases the test was performed (as identified above) or adequately substituted for by a routine annual test a little earlier or later. A few missing ET tests relate to patients who were withdrawn so early in the study that the tests are of no possible relevance (see cases 19 and 24) and in one case the test demanded by Apotex could hardly have been carried out since the patient was dead.

My conclusion once again, must be that the Apotex allegations are almost entirely baseless and reflect failure to study the records and the protocols with sufficient care.

3.7 Allegations regarding other matters

Finally, in its Appendix 15.2.2.3, to the study report, Apotex alleges that miscellaneous deviations from protocol occurred in nine other instances.

A. Patients 5, 13, 27 and 59 are stated to have received Septra during the trial. I do not see that this is prohibited by protocol, which in its section 5.3.2 lists the exclusion criteria and makes reference only to the fact that no other investigational drug should be used during the trial. Septra is a combination of trimethoprim and sulfamethoxazole and has been known for thirty years, so it is not an investigational drug. If Apotex means that these patients were being treated for an infectious disease (which would be the indication for treatment with Septra) then even this is not contraindication, unless the patients were so severely ill (or developed such severe reactions e.g. haematological) that it would be improper to include them in the trial. I can see no evidence that this was the case – their haematological and other data provide no grounds to consider them ineligible.

B. It is alleged that patient Nr 2 was treated despite the fact that the baseline neutrophil count was below 1.5 x 109/l. According to the patient data which I have in my possession, the patient fell below this level only once – on November 9th 1993, when it was recorded as 1.43. The patient's reading on the previous day was 2.4 and a month later it was 2.09; it did not subsequently fall below the permitted level. This single reading must have either been a laboratory error or a very brief variation from the norm and cannot be regarded as a reason to withdraw this person from the study.

C. Patient 38 is stated to have entered the trail a month before being informed consent was given. This is formality which can hardly discredit he results. Having entered the trial and subsequently given formal consent, consent at the outset must surely be implied.

D. Patient 49 is stated to have entered the trial under the minimum age of 6 years and 10 months. This is incorrect. I requested the patient's personal data and find an age on admission of more than 6 years and 11 months.

E. Patient 76 is stated to have received desferoxamine only 1-2 nights weekly at baseline instead of the prescribed 3-4 nights weekly. I have sought data on this patient but the person concerned was not treated in Toronto, so the data are not to be found in the Toronto files.

In summary, I can find no evidence that the accusations regarding miscellaneous deviations from protocol are justified. I can only describe them as trivial and far-fetched.

4. OVERALL CONCLUSION

I could summarize my findings by saying that I have not at any point identified such variations from protocol as could be considered, either separately or jointly, so significant as to render the study invalid. In many instances the allegations were entirely baseless, reflecting a misreading of the records and/or the protocol. In most cases there was no deviation whatsoever from protocol; in the bulk of the remainder the conduct of the investigator, staff or patient fell within the normal range of variation which in clinical work had to be accepted. In a very small number of instances the deviation was such that as to be only marginally acceptable but not remotely such as to undermine what was throughout a conscientiously conducted study.

Such deviations as occurred are entirely trivial as compared to the grave suspicion of harm and inefficacy which began to emerge from the study of deferiprone while Dr. Olivieri was conducting it.

It is therefore my firm conclusion that the allegations of Apotex regarding faults in the conduct of the study LA-01 should be set aside.

Signed

M.N.G. Dukes MD MA LLM
Oslo
Norway
November 20th, 2000