Appendix II of the letter from Drs. Olivieri and Gallie

to Dr. Michael Baker 9 April 2019

The following are questions related to the medical care of UHN patients. We propose these as the minimum considerations to be addressed and answered in a comprehensive Inquiry.

How many, and which, UHN patients beginning in 2009 up to February 2015 (under the management of Drs. Richard Ward, Kevin Kuo, Erik Yeo, and others) were:

- Switched from regimens of first-line, licensed, iron-chelating drugs (deferoxamine, deferasirox) to a regimen involving unlicensed deferiprone.[1]
- Switched to a regimen involving unlicensed deferiprone in which deferiprone was co-**administered with lower-than-therapeutic** doses of first-line agents ("combination" therapy, a non-approved practice).
- Switched to a regimen involving unlicensed deferiprone in which deferiprone was co-**administered with full** doses of first-line agents [as above a non-approved practice).
- Switched to a regimen involving unlicensed deferiprone **monotherapy**.
- Were permitted to draw upon a foreign (non-Canadian-supplied) source of deferiprone (from Greece, or another country) while the drug was unlicensed in Canada?

How many, and which, UHN patients were after February 2015, under the management of Drs. Richard Ward, Kevin Kuo and Erik Yeo and others, maintained on a regimen involving deferiprone (licensed as third line, "last resort" therapy at Health Canada in February 2015):

- A regimen involving last resort deferiprone in which deferiprone was co-administered with lower-than-therapeutic doses of first-line agents ("combination" therapy, a non-approved practice).
- A regimen involving last resort deferiprone in which deferiprone was co-administered with full doses of first-line agents [as above a non-approved practice).
- A regimen involving last resort deferiprone in which deferiprone was prescribed as monotherapy.

[1] In this period, deferiprone was licensed in Europe only as last-resort therapy (its status of licensing worldwide - not to beintroduced unless both effective first line drugs have failed).

Documentation of alleged "failure of licensed therapy"

Prior to introduction or continuation of a regimen involving deferiprone in how many and in which UHN patients:

- Was/is there documentation that one first-line, licensed drug (deferoxamine, or deferasirox), prescribed at recommended doses without addition or interruption, over at least one year, had "failed" to reduce body iron as measured by (the only proven) quantitative measurement, liver iron concentration, compared at baseline and after at least 12 months and showed that liver iron concentration:
    - Did not decline to or was not maintained at concentrations ≤ 7 mg/g dry weight; or
    - Did not decline ≥30% from baseline if baseline liver iron exceeded 15 mg/g
- When "failure" of effectiveness as above, was documented with one licensed drug, was the *second* licensed drug, prescribed at recommended doses without addition or interruption over at least one year, and was "failure" / lack of effectiveness assessed (as defined above) using liver iron concentration (compared at baseline and after at least 12 months).
- Was there documentation that the *second* licensed drug at recommended doses without addition or interruption over at least one year had "failed" (as defined above) to reduce body iron evaluated with liver iron concentration compared at baseline and after at least 12 months.

Documentation of "failure"

Prior to introduction of a regimen involving unlicensed deferiprone, in how many and in which patients treated with licensed therapies at recommended doses without addition or interruption over at least one year:

- Were pre-deferiprone values of liver iron (± cardiac T2*) consistent with acceptable control of body iron, and/or improving relative to the previous assessment.[2]
- Was deferiprone introduced following pregnancy (during which chelation therapy is, in compliancc with all guidelines, deliberately withheld for safety reasons predictably resulting in elevation of liver iron).[3]
    - (In patients switched to deferiprone following pregnancy) was there documentation of intolerance to, or "failure" or "unsuitability" of, both licensed agents.
- (In patients in whom pre-deferiprone liver iron was elevated above the threshold for cardiac disease and early death (15 mg/g)), were doses of deferoxamine/deferasirox prescribed below-recommended-doses for this level of iron burden.[4]
- In patients in whom pre-deferiprone liver iron was elevated above the threshold for cardiac disease and early death (15 mg/g)), were deferoxamine/deferasirox prescribed in doses below-recommended for this level of iron burden, and was this under-dosing justified in the EMR.
- Was a reduced T2* recorded as the "indication" for a switch to unlicensed deferiprone.
    - Was an increase (i.e. improvement) in cardiac T2* recorded during licensed therapy, prior to a swuitch to deferiprone.[5]

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[2] **We identified 16 patients in whom pre-deferiprone HIC and T2* was consistent with excellent control of body iron**. Moreover ,prior to deferiprone in 12 (75%) of these 16 patients, T2* had already increased during licensed therapies; in another 19%, T2* had remained stable. In the 16th patient, T2* had declined (22 to 16 msec) during a year of *inadequate deferasirox*. We were unable to determine why deferiprone was introduced in any of this (largest) group of patients in whom most body iron parameters were improving or stable during licensed first-line drug regimens. Please see PLoS paper.

[3] **We identified three patients, in whom pre-deferiprone liver irons were substantially elevated** [39.4 ± 4.5 mg/g], while T2* was acceptable: in none were deferasirox and deferoxamine documented to have "failed" or was "unsuitable or unavailable". All were iron loaded ***following pregnancy*** during which all chelation therapy had been *deliberate*ly withheld for 9-12 months. We were unable to determine why deferiprone was indicated in this group.

[4] **We identified 13 patients in whom pre-deferiprone liver iron concentrations were elevated** (with normal T2*s). Prior to deferiprone in 31%, liver iron had already declined by nearly 100% and T2* had increased or was stable during licensed therapy. **Many patients had been, for unknown reasons, prescribed doses of deferoxamine/deferasirox below those recommended for these high levels of body iron**. Responses to these inadequate doses of licensed drugs were predictably modest. We were unable to determine why the failure of iron to decline during lower-than-recommended doses of licensed therapy represented an indication for a third-line drug. Please see PLoS paper.

[5] We identified nine patients in whom T2* was reduced (abnormal) prior to the switch to deferiprone: In four, liver iron was optimal; in another four, liver irons exceeded 40 mg/g, among the highest recorded. (Liver iron in the 9th was obtained only six months *after* deferiprone was introduced). T2* was reduced (estimating high levels of cardiac

- Did cardiac T2* "fail" to increase (improve) in the face of sustained maintenance (≥ 18 months) of liver iron concentration to ≤ 7 mg/g.
- Was an isolated descent of "cardiac" iron observed when total body iron failed to decline to ≤ 7 mg/g.

To understand the significance of the questions above, understanding of an acknowledged, fundamental principle of chelation therapy is required. No 'isolated' change in cardiac T2* (which is an *estimate* of "cardiac iron" upon which reliance should not be unqualified) is expected if, and while, total body iron (reflected in liver iron concentration, the only measurement directly *correlated* with total body iron) remains elevated within unacceptable range.[6] Changes in T2* occur more slowly than changes in liver/body iron; they are observed as liver/body iron declines into acceptable range, but they do not occur *contemporaneously* with changes of liver iron. What this means is that (i) even if liver/body iron increases to unacceptably elevated levels, cardiac T2* may not immediately decline (worsen), because of a "lag" period; T2* will eventually begin decline/worsen if elevations in liver/body iron are sustained. Similarly (ii) if liver/body iron had been previously elevated, but begin to decline into acceptable range, cardiac T2* may not immediately increase/improve (a "lag" period) but will eventually increase/improve *if* adequate reductions in liver/body iron are sustained, usually requiring 12-18 months. The absence of change in T2* if liver/body iron is elevated is not a "failure" of therapy but means that total body iron must be reduced. Similarly, an absence of immediate change in T2* as liver/body iron declines after periods of unacceptable elevations does not represent a "failure" of therapy. **The important point is**: no scientific or medical justification exists for pronouncing a patient to have "failed" a regimen because T2* fails to improve when: (i) liver/body iron remains unacceptably elevated; or (ii) liver/body iron has previously been unacceptably elevated, but is now declining into acceptable range (≤ 7 mg/g) but has not been at that acceptable range for 12-18 months. **T2* changes are anticipated if declines in liver/body iron are *sustained* but they are not immediate.**[7]

Toxicity with Licensed therapy:

Prior to introduction of a regimen involving deferiprone in how many and in which UHN patients was there documentation that:

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iron) in eight of the nine; in a 9th patient, T2* was determined only six months *after* deferiprone was introduced. Four patients had experienced *improvements* in T2* during licensed therapies; in another three, T2* was *stable* during licensed therapy. In the last patient, T2* had declined on low doses of deferasirox (at 50% of recommended dose). In some of these patients, we presume that deferiprone was introduced to attempt to preferentially reduce "cardiac" iron, despite the lack of evidence (FDA; Cochrane) to support such a practice. In the four patients with liver iron concentrations > 40 mg/g (fifth patient, unknown), we were unable to determine why judicious reduction of *total* body iron burden with licensed drugs was not pursued. Please see PLoS paper.

[6] There is an elevated risk of cardiac disease, glucose intolerance and premature death at liver iron concentrations exceeding 15 mg/g liver dry weight, elevations of liver irons between 7 and 15 mg/g increase the risk of other serious complications, and ideal range sought in therapy is 3 to 7 mg/g. Estimates of *elevated* "cardiac iron" by T2*, are reflected by contrast by *reduced* values (less than 10 msec); improvements are reflected by *increases* in T2*. Please see PLoS paper.

[7] The FDA and Cochrane have confirmed that there is no evidence for a magical, rapid, isolated, "preferential" reduction in "cardiac iron" induced by deferiprone, or any other drug. Simply stated, if liver/body iron is elevated, T2* does not improve in isolation. The FDA ruling firmly rejecting such claims by Apotex is consistent with the recognized processes of cardiac and liver iron loading and unloading.

- A first-line licensed drug had resulted in **serious adverse effect(s)** preventing continued administration of the first licensed drug.
- The second licensed drug had resulted in **serious adverse effect(s)** preventing continued administration of the second licensed drug.
- SAE(s) observed were related temporally to increase(s) in the dose of the licensed drug. If so, was there documentation in the EMR that a dose increase was medically indicated (evidence of inadequate effectiveness [increasing liver iron concentration] at a previous lower dose). If so, was there documentation the dose increase was appropriately gradual (10% increase in dose over one month, another 10% increase over the second month; or was the dose of licensed therapy increased abruptly (≥30% in one day).
- Genuine efforts had attempted to manage an SAE allegedly occurring as a result of licensed therapy, including: (i) confirming that the SAE was not a result of another factor (for example: an increase in serum creatinine developing during deferasirox in a patient later confirmed to have renal carcimona; 'bloating' developing during deferasirox, in a patient later confirmed to have severe biliary tract disease whose symptoms were responsive to cholecystectomy); (ii) that the SAE was not transient; (iii) that the SAE was not responsive to temporary withdrawal or temporary dose reduction.
- Documentation of SAEs arising during licensed therapy were pertinent at the time (2009 to 2015) at which unlicensed deferiprone was introduced.8

Poor patient 'compliance' with licensed therapy

- Prior to introduction of a regimen involving deferiprone in how many and in which UHN patients was there documentation:
- That both first-line licensed drugs were associated with inadequate compliance, such that the continued administration was not indicated.
- That counseling strategies, including dedicated social work or psychologic consultation, had focused on providing full information to patients about compliance with licensed therapy.

Outcomes of deferiprone

During exposure to a regimen involving deferiprone, in how many and which UHN patients:

- Received deferiprone in excess of 100 mg/kg/day.
- Did, and did not, undergo weekly monitoring of complete blood counts.
- Marrow toxicity:
    - Developed neutropenia or agranulocytosis requiring hospitalization and G-CSF.

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[8] For example, in how many and in which patients was deferoxamine-associated high-frequency hearing loss cited as a reason to abandon deferoxamine? (This adverse effect, reported years ago [Olivieri et al NEJM 1986]), had been managed without needing to withdraw deferoxamine in any affected patients over the subsequent two decades. Hence, it cannot (in our view) truthfully be cited as an indication for the switch to deferiprone in 2009.

  - Were managed following neutropenia or agranulocytosis in accordance with recommendations (ie immediate withdrawal of deferiprone; future re-challenge contra-indicated).
  - Were re-exposed to deferiprone, despite having already sustained deferiprone-induced agranulocytosis during a first exposure.
  - Were re-exposed to deferiprone, despite having already sustained deferiprone-induced agranulocytosis during a second exposure.
- Liver Dysfunction:
  - Did liver dysfunction (*elevations of serum ALT two-fold or more over baseline*) develop one to six months following exposure to deferiprone, or following increases in deferiprone dose.
  - Was liver dysfunction recorded as an adverse effect of deferiprone in the EMR.
  - Was liver dysfunction permitted to persist without alteration in the regimen involving deferiprone.
  - Were, after recording of sustained liver dysfunction, continued on deferiprone.
  - Was the relationship of liver dysfunction and deferiprone exposure confirmed, by challenge, withdrawal, and re-challenge of deferiprone.
  - When the relationship of liver dysfunction and deferiprone exposure was confirmed by challenge, withdrawal, and re-challenge of deferiprone, was deferiprone discontinued.
  - Underwent liver biopsy to assess or fibroscan to estimate liver histology.
  - Were patients withdrawn immediately (within six months) if reduction in dose was followed by persistent elevations of ALT
  - Were patients withdrawn after a long period (> 6 months) if reduction in dose was followed by persistent elevations of ALT.
  - How many patients had sustained permanent elevation of serum ALT after deferiprone.
- Arthragias/Arthritis:
  - Developed arthralgias or arthritis following exposure to deferiprone.
  - (Who developed arthralgias or arthritis following exposure to deferiprone), were managed in accordance with recommendations (ie reduction in dose, followed by withdrawal of deferiprone if arthralgias or arthritis persisted)
  - Were arthralgias or arthritis recorded as an adverse effect of deferiprone in the EMR.
  - Were continued on deferiprone after deferiprone-associated arthralgias or arthritis.
  - Complained of arthralgias or arthritis after discontinuation or continuation of deferiprone.
  - Who were withdrawn immediately (within six months) if reduction in dose was followed by persistent arthralgias or arthritis
  - Who were withdrawn after a long period (> 6 months) if reduction in dose was followed by persistent arthralgias or arthritis.
  - Sustained permanent symptoms of arthralgias or arthritis after deferiprone.
- Diabetes:

  - Did new diabetes develop following exposure to a regimen involving deferiprone.
  - Was the onset of new diabetes recorded as an effect of inadequate control of iron by deferiprone in the EMR.
  - (Who developed diabetes) did DM develop after elevations of liver iron concentration over 15 mg/g, the threshold for glucose intolerance, had developed or remained at this level after the introduction of deferiprone.
- Chelation Effectiveness:
  - Did liver iron increase to > 15 mg/g.
  - Did liver iron originally at > 15 mg/g prior to deferiprone decline to optimal values (3-7 mg/g)
  - Were permitted to maintain liver iron concentration > 15 mg/g for greater than one year without return to full doses of first line licensed drugs
  - Were increases/improvements in cardiac T2* observed if liver iron concentration remained > 15 mg/g.
- Alternations in Transfusions:
  - Were alterations in transfusion intensity implemented (to attempt to ameliorate myocardial iron) following the switch to deferiprone (i.e. was the patient transfused less intensely after a regimen involving deferiprone was introduced).
  - Was a plan to reduce the volume of transfused blood (to attempt to ameliorate myocardial iron) loading documented in the EMR.
- Experimental Therapeutic combinations:
  - Was deferiprone combined with deferasirox, an unproven experimental combination.
- Death:
  - Died.

Responsibilities of a physician under the Special Access Program

Were the responsibilities (of a physician under Health Canada's Special Access Program) [under which deferiprone was provided over six years in > 40 UHN patients] fulfilled by Drs. Ward, Kuo, Yeo and others, in switching patients to deferiprone from 2009 to February 2015: *Please refer to:* *https://www.canada.ca/en/health-canada/services/drugs-health-products/special-access/drugs/guidance-industry-practitioners-special-access-programme-drugs-health-canada-2008.html*

- Was the SAP used as a mechanism "to encourage the early use of drugs or to circumvent clinical development of a drug or regulatory review of a submission for marketing."
- Was their seeking of access to deferiprone through the SAP "limited in duration and quantity to meet emergency needs only."
- In the event that a drug submission for deferiprone was under regulatory review (in the case of deferiprone application had been ongoing in Canada by Apotex and Dr. Ward and Yeo, since at least 2012) "was access to deferiprone limited until that review had been completed."

- Were UHN patients informed by the phsyicians that "drugs accessed through the SAP do not undergo the scrutiny of a benefit-risk assessment provided within the regulatory framework applied to new drug submissions or clinical trial applications."
- Were UHN patients informed by the phsyicians that "authorization through SAP does not constitute an opinion that a drug is safe, efficacious or of high quality."
- Did Drs. Ward, Kuo, Yeo and others who initiated a SAP request for deferiprone from 2009 to February 2015 fulfill the responsibilities of a practitioner [see 2.2 Practitioners]as follows:
    - Seek informed consent from each patient?
    - Report the results of deferiprone therapy including any AEs encountered?
    - Provide an accounting for all drug supplies received?
    - Ensure that the decision to prescribe deferiprone was supported by credible evidence in for each patient (including an investigator's brochure, prescribing information from another jurisdiction [Europe and USA in the case of deferiprone; see footnote 13] or publications in the medical literature)?
    - Provide patients with information about the drug's potential risks and/or benefits as well as alternative therapies available?
- Were the responsibilities of a physician fulfilled by Drs. Ward, Kuo, Yeo and others from 2009 to February 2015 [with respect to "4.2 Consideration"] under Health Canada's Special Access Program [under which the EMRs showed deferiprone was provided over six years in > 40 UHN patients] of which patients were switched to deferiprone as follows:

  4.2 Consideration "Consideration is the process by which the SAP decides whether authorization is appropriate and justified. Each request represents a unique set of circumstances and is supported to varying degrees by information provided by the practitioner. Consideration takes into account and balances the following factors to ensure that an emergency exists and there is credible data to support the request"

Did Drs. Ward, Kuo, Yeo and others who initiated a request for deferiprone from 2009 to February 2015 provide adequate information on:

- Seriousness of disease relevant to the request:
    - "Description of the medical emergency for which the drug is requested".[9]
- Clinical status of patient:
    - "Description of current clinical status of the patient, including prognosis."[10]
- Other therapies tried and/or ruled out:
    - "Summary of marketed therapies that have failed, have been considered, ruled out or are unavailable".11

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[9] We were unable to determine the existence of a medical emergency in a patient switched to deferiprone at UHN.

[10] We were unable to determine clinical instability in a patient switched to deferiprone at UHN.

- Prior patient experience with the drug:
    - "including a summary of a patient's past experience with the drug, including evidence of efficacy and adverse drug reactions".12

[11] We were unable to determine that any UHN patient switched to deferiprone had failed licensed therapies.

[12] We were unable to determine that in any UHN patient switched to deferiprone after 2009, the previous failure of deferiprone (between 1989 to 1996 when two Toronto clinical trials in which these patients participated were prematurely terminated by Apotex which were available in the medical records of each patient) were provided to Health Canada or discussed with the patient.

- Did Drs. Ward, Kuo, Yeo and others who initiated a request for deferiprone from 2009 to February 2015 provide adequate information to patients they switched including:
    - Prescribing information/package insert from the jurisdiction where the drug may be marketed.[13]
    - Record Keeping: Did Drs. Ward, Kuo, Yeo and others who initiated a request for deferiprone from 2009 to February 2015
- Maintain all records for a period of 25 years, in a manner that permits rapid retrieval if necessary.[14]

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[13] When first-line licensing was first pursued, Europe instead imposed second-line restrictions "because comprehensive information on safety and efficacy cannot be provided."[89] Ten years later, the FDA refused first-line approval, and approved deferiprone as third-line therapy only, because of a "failure to provide answers to [the FDA's] questions on efficacy and safety."[84] FDA's approval of deferiprone, the agency's first approval not to require evidence from a "adequate well-controlled clinical trial or a validated surrogate marker,"[90] has been described as a "recklessly dangerous precedent."[91] The FDA drug monograph confirms that "no controlled trials of deferiprone demonstrate a direct treatment benefit."[86]

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86. Ferriprox Product Monograph. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021825lbl.pdf.

87. Swedish Orphan International. 2006.

88. Spino M, Piga A. Use patent for deferiprone. US20030311814 on 2003-04-04. 2006.

89. Deferiprone Marketing Approval. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000236/human_med_000789.jsp&mid=WC0b01ac058001d124

90. Pazdur R. Complete Response to Application for Ferriprox. 021825 Orig1s000 November 30, 2009.

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[14] If this was fulfilled the information should be immediately and easily available to "UHN officials" as we have repeatedly urged.