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Attention: Melissa Kostopoulos

ASX Compliance Pty Ltd
Level 4, North Tower, Rialto
525 Collins Street
Melbourne VIC 3000

By Email: Melissa.Kostopoulos@asx.com.au

30 December 2022

Dear Melissa,

Starpharma Holdings Limited (ASX:SPL) – Aware Query Request for Information

Before addressing the specific ASX questions we would like to clarify:

- the nature of the AZD0466 clinical trial which is the subject of Starpharma's ASX announcement as this will assist ASX in understanding the materiality of results at different stages of the trial; and
- the sequence of events, as there appears to be a misunderstanding in your letter dated 20 December 2022 (**Aware Letter**) about the nature of information presented by AstraZeneca at different times.

Dose escalation in clinical trials

By way of background the AZ *Phase 1/ 2 clinical trial of AZD0466 as Monotherapy for Patients with Advanced Haematological Malignancies* is currently in the "dose escalation" phase of the trial. Dose escalation is a clinical study design that is frequently used for the first use of a drug in humans and it allows the safe dose of a new drug to be determined. In a doseescalation study, the dose of the test drug starts very low and is increased a little at a time in small groups of patients until the highest dose that does not cause harmful side effects (referred to as dose limiting toxicities or DLTs) is identified. This stepped and conservative increase in dose is especially important for novel compounds which have the potential for toxicities.

The first patient cohorts in a dose escalation trial are given very low doses of the drug initially and then the patients are monitored for toxicities for a defined period (typically several weeks). If the drug is well tolerated, then doses are progressively increased with each dose level higher than the last. This means that the significance (or, in other words, materiality) of good tolerability and the lack of DLTs is greater as the dose level increases, and as the patient numbers in each group increase. On the other hand, the initial (low dose, sub therapeutic) groups would typically be expected to have lesser chance of toxicity than the higher doses. In addition, small numbers of patients at a given dose are of lesser significance than a completed dose cohort. As such, the results from the earlier stages of the dose escalation phase of a trial are of less significance or materiality.

To summarise, as the dose increases the likelihood of toxicity increases so the finding of no DLTs at higher dose groups is increasingly significant or material, particularly given the toxicity of this class of drug absent the DEP platform. In addition, until a patient has been both dosed *and* followed for the full DLT period, being a period of 35 days after first dosing for that patient and 28 days in this instance for further dosing escalations for that patient, the findings of that dose group is incomplete and less significant in understanding the tolerability of the drug.

Timeline of events

As outlined above, we would also like to clarify the sequence of events as there appears to be an assumption in your letter that certain information was released publicly by AstraZeneca earlier than was in fact the case. Given this, we've set out a brief timeline below to assist in clarifying matters. For simplicity, we have presented all times in the timeline in Australian Eastern Daylight Savings Time (AEDT) given that is the time zone that is relevant for ASX's purposes in considering the sequence of events:

1 November 2022 (AEDT)
Starpharma receives an early draft of the poster to be presented at ASH which omits certain tables and graphs. This is stated to be subject to further review and verification by AstraZeneca.

Over the following period of 2 weeks or so, SPL received further drafts of the poster but all of these remained in draft form and subject to further review and/or change by AstraZeneca prior to the publication. Despite requesting it, SPL did not receive a final version of the poster from AstraZeneca prior to publication as outlined below and so at no stage prior to 13 December held a version of the poster that it knew to be final and complete.

At some stage on or prior to 11 November 2022 (AEDT)
An abstract was published on conference website for ASH's annual meeting and exposition in New Orleans in the USA (**Abstract**). The Article appears to be a printed version of the Abstract. An Abstract contains all text, whereas a scientific poster contains figures and/or tables to allows reader to comprehend the major points of the research and to understand the significance of the work. The Abstract is a short (250-350 word) summary of a poster and must omit all tables and graphs

11 November 2022 (AEDT)
We became aware of the Abstract and it was circulated internally for review.

The Abstract was a high level and incomplete account of what was proposed to be included in the poster to be published in December 2022. The data on hand at the time of submission of the Abstract was from 31 May 2022 (and so quite limited and dated).

At the time of publication of the Abstract, only 9 patients had been treated and only at the lowest dose groups - 300 mg (4 patients), 600 mg (4 patients), and 1200 mg (1 patient). These were the initial doses in the dose escalation plan for the clinical trial and only 7 of the

9 patients had been followed for long enough to complete the DLT evaluation period, being the period of 28 or 35 days for which patients are monitored to assess for adverse events associated with the dosing. Importantly, one of the patients that hadn't completed the DLA evaluation period will have been the patient dosed at 1200mg. The Abstract also only contained a brief description of adverse events, which is not unexpected given it is an abstract.

After submission of the Abstract, the trial continued to enrol patients, including 6 additional patients in the higher 1200mg dose group and 3 additional patients in the higher 2400 mg dose group, with the intent that the poster would have updated and more complete data available, including through the completion of DLT evaluation periods at higher dosing levels.

15 November 2022 (AEDT)
The Article referred to in paragraph F of the Aware Letter was published in the ASH Journal, Blood. We were not aware of the publication of this Article until we received the Aware Letter.

29 November 2022 (AEDT)
The AGM Presentation referred to in paragraph E of the Aware Letter was released by SPL to provide a general update on progress to shareholders.

The AGM Presentation combined information from a verbal update with AstraZeneca on 10 November 2022 and information from the Abstract. The verbal update was limited but included that the number of enrolled patients had increased to 18 and that there remained no DLTs. There was no further new or detailed information shared with us by AstraZeneca during the verbal update. We did not include additional detail from the draft poster at this stage as we could not confirm that that information was final, accurate and complete and it also remained confidential at that time.

12 December 2022 (AEDT)
The Aware Letter also refers in paragraph D to "AstraZeneca's "Emerging AstraZeneca Hematology Pipeline" session at the 2022 ASH Annual Meeting Program and suggests that this was the first time that the updated and more detailed data relating to the AZD0466 clinical trial was publicly released. This is not the case.

This presentation was an industry sponsored session at the ASH conference where AstraZeneca briefly presented on a number of products from their haematology pipeline. AZD0466 was one of the products mentioned – and the presentation was solely on the AZD0466 trial design – which was already in the public domain and also accessible on clinicaltrials.gov website.

For clarity, we will refer to this as the Promotional Presentation in the balance of this letter.

13 *December 2022 (AEDT)*

- **8.00am** – Starpharma convened a meeting in preparation for the release of the poster. As flagged above, we did not see a final version of the poster and were unaware of whether there would be changes to the information previously provided and whether they would have a positive or negative impact on the preliminary results being reported in the poster.

- **8.56am** – Due to challenges in locating the poster on the ASH conference website, Starpharma first accessed a copy of the final poster from the ASH conference website at 8.56am by way of a download. It should also be noted that access to the material was restricted to registered ASH meeting delegates only.

- **11.00am** - The poster was presented at the ASH conference on Tuesday 11.00 am to 1.00 pm Tuesday 13 December 2022 AEDT, being 6.00 to 8.00pm on Monday 12 December 2022 (CST). This presentation is the formal presentation of the scientific poster on the AZD4066 trial referred to in paragraph C of the Aware Letter. For clarity, we will refer to this as the Poster Presentation for the balance of the letter.
  - The Poster Presentation provided the latest clinical data from the AZD0466 Phase1/2 clinical trial, as at 13 October 2022 (the version on the website erroneously recorded the data as being at 24 September 2022). The updated data included additional information on the actual doses administered and the number of patients at each dose and the responses observed.
  - As the focus of the dose escalation phase of the clinical study was safety and tolerability, the poster showed the following;
    - 18 patients had now been treated - 300 mg (4 patients), 600 mg (4 patients), 1200 mg (7 patients) and 2400mg (3 patients). Previously the information available in the Abstract/Article was only the initial lowest doses 300 mg (4 patients), 600 mg (4 patients), 1200 mg (1 patients). The new data therefore included an additional 6 patients in the 1200mg group, a dose which was 4 times the starting dose, and it also included 3 patients in the 2400mg group, a dose which was 8 times the starting dose.
    - No dose limiting toxicities (**DLTs**), treatment-related serious adverse events (**TRAEs**), treatment-related deaths, or adverse events (**AEs**) leading to treatment discontinuation had been observed

- **11.08am** - Starpharma released its ASX announcement entitled "Positive AZD0466 Clinical Data Presented by AstraZeneca". The content of the announcement reflected the key points from the poster/Poster Presentation .

To be clear, the Poster Presentation was not presented on 11 December as the poster footer indicated. This appears to be a dating error.

In reference to your letter dated 20 December 2022, please find answers to your request for information:

1. *Does SPL consider the preliminary results from the ongoing AZD0466 clinical trial to be information that a reasonable person would expect to have a material effect on the price or value of SPL's securities?*

   Yes, but only once the information was sufficiently complete and detailed to have clinical significance which we considered to be at the time of the Poster Presentation. As outlined above, while the two line summaries from the Article/Abstract and the Poster Presentation quoted in the Aware Letter are essentially the same, the information disclosed in the Article/Abstract and available to Starpharma at the AGM was qualitatively different to the information disclosed in the Poster Presentation.

   At early stages of the dosing phase of a clinical trial, which is the period the subject of the Abstract, the data lacks significance or materiality given that the patient numbers are low, the doses are low and not expected to cause DLTs and the DLT evaluation period on higher doses has not been completed. This means that no conclusions on tolerability can reliably be drawn. At later stages of the trial, and so in our view when the Poster Presentation was made, the data begins to become significant or material even if the trial is not complete as the doses have increased many fold, DLT evaluation periods have completed and patient numbers are increased.

To summarise, information released during a clinical trial process is of escalating value and it is not the case that only the final results should be considered material.

2. *If the answer to Question 1 is "yes":*

2.1. Please provide the basis for this view.

See reasoning set out above.

2.2. Noting that preliminary results from this ongoing AZD0466 clinical trial were publicly available from at least 15 November 2022 (see paragraph F above):

2.2.1. Please advise when SPL first became aware of the preliminary results that were disclosed in the Presentation, the AGM Presentation and the Article, respectively.

As outlined above, it is important to differentiate between the information available at different stages as while the information relates to preliminary results in each instance, it is qualitatively different at different stages.

We became aware of the Abstract on 11 November 2022.

We were provided with a verbal update from AstraZeneca on 10 November 2022, which we combined with the information from the Abstract, to provide the update including the AGM Presentation.

We were provided with a draft of the poster by AstraZeneca for review purposes on 1 November in parallel with detailed review by AstraZeneca and the poster authors but the final version released by AstraZeneca, which contained updated data was first available to us for download on the morning of Tuesday, 13 December 2022 AEDT and was presented by AstraZeneca at 11am on the same day at the Poster Presentation. At no stage prior to this, and despite a request, was Starpharma provided with a final version of the poster by AstraZeneca that it could accept as being accurate and complete.

2.2.2. Please advise whether or not SPL was aware of the publication of the Article. If the answer is "yes", please advise when SPL first became aware of the Article's publication.

SPL was not aware of the publication of the Article on 15 November 2022 but was aware of the Abstract from 11 November 2022 and, as outlined above, the Abstract includes the same information as the Article.

2.2.3. Please explain why details of preliminary results from the AZD0466 clinical trial were not released on MAP earlier.

The Article/Abstract:

- only contained data relating to the first 9 patients who had received a dose;
- for all but one of the patients, the doses were low and what we considered sub-therapeutic and so, in our view, no meaningful conclusions on tolerability could be reliably drawn from the data disclosed in the Article; and
- only 7 of the 9 patients had been followed for long enough to complete the DLT evaluation period, being the period for which patients are monitored to assess for adverse events associated with the dosing. In particular, the 1200mg patient had not completed the DLT evaluation period.

Accordingly, at these very low doses, with small patient numbers (only one in 1200mg) and with only 7 patients at the lower dosing levels to have cleared the DLT evaluation period, the lack of DLT's could not be considered significant/material at this stage.

In our view, the preliminary results disclosed in the Poster Presentation were significant/material, particularly given that potential toxicity of this class of drugs absent the DEP platform, despite still being preliminary results. Accordingly, details of those results were released on MAP immediately (or at least as soon as practicably possible) after the final poster was available to SPL and released publicly by AstraZeneca.

3. *If the answer to Question 1 is "no", please provide the basis for this view.*

Not applicable.

4. *Does SPL consider the information in the Announcement that AstraZeneca had made a poster presentation concerning preliminary results of the AZD0466 clinical trial to be information that a reasonable person would expect to have a material effect on the price or value of SPL's securities?*

Yes, SPL considers the information in the Announcement to be information that a reasonable person would expect to have a material effect on the price or value of SPL's securities. To be clear, this is the Poster Presentation on Tuesday, 13 December 2022 AEDT that is material and not the earlier Promotional Presentation.

5. *If the answer to Question 4 is "yes":*

5.1. Please provide the basis for this view. In doing so, please:

5.1.1. Identify the new and material information in the Announcement, particularly in relation to the information previously disclosed in SPL's AGM Presentation (see paragraph E above).

As outlined above, at the time of the AGM Presentation SPL was relying on the Article/Abstract and the verbal update from AstraZeneca which represented a limited and very early data set from the dosing phase of the AZD4066 clinical trial.

At the time of the Announcement, SPL had the benefit of a final and complete data set which it considered to be qualitatively different to the data available at the time of the AGM Presentation. Those differences included:

- Details of the dosing for the 18 patients treated at that time, being 300 mg (4 patients), 600 mg (4 patients), 1200 mg (7 patients) and 2400mg (3 patients) compared to the information available in the Article/Abstract which related only to the lowest doses of 300 mg (4 patients), 600 mg (4 patients), 1200 mg (1 patient). The new data therefore included an additional 6 patients in the 1200mg group, a dose which was 4 times the starting dose, and 3 patients in the 2400mg group, a dose which was 8 times the starting dose. These ten extra patients at higher doses and with more DLT evaluation periods completed added substantially to the data set and so significance/materiality of that information.
- Confirmation again that at these higher patient numbers and dosing levels that there were no dose limiting toxicities (DLTs), treatment-related serious adverse events (AEs), treatment-related deaths, or AEs leading to treatment discontinuation had been observed

5.1.2. Comment specifically on ASH's statement that the relevant session is solely promotional in nature (see paragraph D above).

As outlined in the introduction to our letter, there were two presentations at the ASH conference – a Promotional Presentation that included very limited information which was already publicly available and was intended to promote AstraZeneca's product pipeline and a Poster Presentation, which involved a presentation of updated and more progressed data on the AZD4066 clinical trial.

We agree that the Promotional Presentation was simply that, promotional in nature, and that the information disclosed at that presentation did not warrant disclosure on MAP, which is why SPL's release to the market did not occur until the Poster Presentation took place on Tuesday, 13 December AEDT.

5.2. ASX observes that the Presentation was apparently made on Saturday 11 December 2022 (CST) and, accordingly, prior to the commencement of trading of SPL securities on ASX on 12 December 2022. However, the Announcement was only released on MAP following the commencement of trading on the next day, 13 December 2022. Does SPL consider this to be in compliance with SPL's obligation to immediately disclose material information under Listing Rule 3.1? Please provide the basis for this view.

As mentioned previously, the Presentation referred to by ASX in this question is the Promotional Presentation. It was promotional in nature and disclosed no material information that would have warranted release on MAP.

The final poster was first available to SPL and other conference attendees on the morning of Tuesday 13 December 2022 AEDT by way of a download from the ASH conference website and SPL then proceeded to release an announcement on MAP as soon as practicable, which occurred at 11.08am on Tuesday 13 December 2022 AEDT. This was shortly after the Poster Presentation commenced at the ASH conference.

From market open on Tuesday 13 December 2022 AEDT to the release of the Announcement, SPL was monitoring trading, with only one "crossing trade" occurring during this time. SPL promptly, and without delay, released the Announcement on MAP. Accordingly, in respect of the Announcement, SPL confirms it was in compliance with its obligation to immediately disclose material information under Listing Rule 3.1.

5.3. Please explain why SPL did not release an announcement on MAP concerning the publication of substantially similar conclusions in the Article (see paragraph F above).

As outlined above, while the brief summary from the Article/Abstract and the Poster Presentation are substantially the same, the data set supporting those conclusions are qualitatively different once considered in detail. In particular, the Article/Abstract:

- only contained data relating to the first 9 patients who had received a dose;
- for all but one of the patients, the doses were very low and what we considered sub-therapeutic and so, in our view, no meaningful conclusions on tolerability could be reliably drawn from the data disclosed in the Article; and
- only 7 of the 9 patients had been followed for long enough to complete the DLT evaluation period, being the period for which patients are monitored to assess for adverse events associated with the dosing.

Accordingly, at these very low doses, with small patient numbers and with only 7 to have cleared the DLT evaluation period, in SPL's view the lack of DLT's could not be considered significant/material at this stage.

5.4. *To the extent that SPL believes there is a difference between the preliminary results disclosed in the Presentation, the AGM Presentation and the Article, respectively, or between the manner of publication of those results (or both), for the purposes of its continuous disclosure obligations under the Listing Rules, please provide the basis for why it considers any such difference(s) to be material for these purposes and, in particular, Listing Rule 3.1.*

As previously mentioned, while the two sentence summary is consistent across the Article/Abstract, the underlying data is qualitatively different which, in our view, justified the different disclosure position taken by SPL in relation to the Article/Abstract, the AGM Presentation and the Poster Presentation.

We appreciate it is repetitive but, at the time of the Announcement/Poster Presentation, SPL had the benefit of a more advanced data set which it considered to be qualitatively different to the data in the Article/Abstract and available at the time of the AGM Presentation. Those differences included:

- Details of the dosing for the 18 patients treated at that time, being 300 mg (4 posters), 600 mg (4 posters), 1200 mg (7 posters) and 2400mg (3 posters) compared to the information available in the Article/Abstract which related only to the lowest doses of 300 mg (4 posters), 600 mg (4 posters) and 1200 mg (1 poster). The new data therefore included an additional 6 patients in the 1200mg group, a dose which was 4 times the starting dose, and 3 patients in the 2400mg group, a dose which was 8 times the starting dose.
- Confirmation again that at these higher patient numbers and dosing levels that there were no dose limiting toxicities (DLTs), treatment-related serious adverse events (AEs), treatment-related deaths, or AEs leading to treatment discontinuation had been observed.

6. *If the answer to Question 4 is "no":*

6.1. *Please provide the basis for this view.*

Not applicable

6.2. *Please explain why SPL marked the Announcement as "market-sensitive" when lodging it on MAP.*

Not applicable

6.3. *Does SPL consider that the Announcement contravened ASX's guidance on "ramping announcements" (see paragraph J above)? If not, please provide the basis for this view in light of the increase in the price of SPL's securities on 13 December 2022 (see paragraph B above).*

Not applicable.

6.4. *Does SPL consider the release of the Announcement to be an appropriate use of MAP (see paragraph K above)? Please provide the basis for this view.*

Not applicable. However, for completeness, SPL considers the release of the Announcement on MAP appropriate. The Announcement is factual and not worded

in an exuberant manner and involves the disclosure of information that a reasonable person would expect to expect to have a material effect on the price or value of SPL's securities.

7. *Does SPL consider that it has the appropriate policies or procedures in place to ensure compliance with its continuous disclosure obligations? Please outline any planned improvements to SPL's policies and procedures.*

   Starpharma considers that it has the appropriate policies or procedures in place to ensure compliance with its continuous disclosure obligations.

8. *Please confirm that SPL is complying with the Listing Rules and, in particular, Listing Rule 3.1.*

   Starpharma confirms it is complying with the Listing Rules, in particular, Listing Rule 3.1.

9. *Please confirm that SPL's responses to the questions above have been authorised and approved in accordance with its published continuous disclosure policy or otherwise by its board or an officer of SPL with delegated authority from the board to respond to ASX on disclosure matters.*

   Starpharma confirms these responses to the questions above have been authorised and approved in accordance with the Company's published continuous disclosure policy.

   This letter has been approved by the Board Chairman, Rob Thomas and CEO / Director, Jackie Fairley.

Yours sincerely,

Nigel Baade
Company Secretary