noctura 400

POLYPHOTONIX

RESPONSE TO THE PUBLICATION OF THE CLEOPATRA CLINICAL TRIAL PAPER

Executive Summary

If a patient does not take a treatment they cannot derive any benefit.

It is instructive to remember this when reviewing the published CLEOPATRA paper.[1]

The paper published in The Lancet Diabetes & Endocrinology Journal, "Clinical efficacy and safety of a light mask for prevention of dark adaptation in treating and preventing progression of early diabetic macular oedema at 24 months (CLEOPATRA): a multicentre, phase 3, randomised controlled trial", reports a negative outcome.

It is scientifically accepted that light therapy works as a treatment for diabetic eye disease. One of the authors, Arden has himself carried out numerous clinical studies in this area[2–4] and our own clinical trials[5,6] and commercial experience with 1 million hours of recorded monitored patient use in multiple countries also supports it. The question arises, if the therapy works and patients are willing to wear the mask, why has this trial failed?

It is known that light therapy is beneficial because it reduces the hypoxic damage that develops during dark adaptation by the rods.[7–10] It follows that to prevent damage, Noctura masks should be worn during most of the patient's full sleep period and regularly each night. Wearing only for only a small portion of a patient's sleeping hours will inevitably lead to dark adaptation and cancel the benefit of this treatment. One of the key distinguishing features of the Noctura mask is that it has a patented technology that monitors patient usage and compliance, which is reported to the prescribing clinician.

PolyPhotonix was not involved in either the design of this trial or its management; however, all of the patient compliance data used in the analysis of this trial was generated and owned by PolyPhotonix. It is clear that patients did not come anywhere close to wearing the mask for the period of time which could be defined as compliant. The arbitrary definition used by the CLEOPATRA team was 70% of a 6-hour night sleeping period, this being 4.2 hours. Thus in the trial 100% compliance would be considered 6 hours of mask use per night. It is important to note that only 7 patients out of 155 in the Noctura arm of the trial achieved or exceeded this threshold limit for the full trial period.

Coaching of patients to wear the mask was clearly minimal and ineffective as patient usage contrasts markedly with our own and others' experience in other trials.[2–6, 11–13] Sadly, this trial has been a wasted opportunity and the reasons for the failure are described below. Contrary to the CLEOPATRA authors' view and linked comment[14] it is clear that better designed and managed studies using Noctura 400 would be of significant value.

If a drug trial only reported 4.5% of patients achieving the compliance threshold in the use of the drug then it would clearly be judged a mismanaged trial. The very low use of the Noctura mask (regardless of the reason) in the Cleopatra trial has the same effect and should be judged in the same way.

There are 4 main areas identified within the published CLEOPATRA paper that are of major concern which are discussed in more detail below:

1. **Questionable Statistical Model Used for Analysis – Median Percentage;**
2. **Very Low Mask Usage/Compliance; Only 4.5% of patients (7/155) enrolled into the trial consistently achieved or exceeded the compliance target**
3. **Patient Management, Communication & Feedback Processes;**
4. **Questionable Interpretation of 12 Month Diffuse DMO Benefit which was Unsustained at 24 Months.**

Background

PolyPhotonix provided the Noctura 400 light-mask along with an adapted sham device into the CLEOPATRA study as requested. Their original plan was to use an alternative development light mask from another company, however due to regulatory discrepancies with the other device PolyPhotonix was asked to step in and agreed to supply the Noctura device. At this stage the trial was fully funded by the NIHR and the protocol agreed. PolyPhotonix had no part in trial management and had agreed to supply patient compliance data to the CLEOPATRA team generated from its own software system 'PPX Works'.

Noctura 400 reads and records patients' nightly use of the mask (patient compliance) and the data is downloaded from each mask via RFID into a cloud based secure software system called 'PPX Works'. Each mask is identified to a particular patient by patient number and so it is possible to track the usage of each individual patient, each night, throughout the 24 month trial period. No patient identifiable data from the trial is stored on PPX Works. The sham mask had the same outer mould and appearance but the circuitry, batteries, and Organic LEDs were removed and replaced with green card. The CLEOPATRA management created an arbitrary minimum threshold compliance level of 70% (see notes below for explanation on CLEOPATRA calculation on compliance threshold). The sham masks were incapable of measuring patient wear.

Noctura 400 has the capability of recording data on the full nightly cycle of up to 8 hours of light treatment. The CLEOPATRA management team decided to adopt 6 hours as being 100% compliant with regards to this study. Therefore, threshold compliance in CLEOPATRA was defined as an average of 70% of 6 hours per night (4.2 hours, or 52.5% of 8 hours). All patients who dropped below this level would be deemed to have low compliance.[1]

It is important to note that true compliance should be regarded as mask use vs number of hours in the dark. The Noctura 400 mask records accurately the time it is worn, but it will not record the time the patient spends in the dark without the mask. In the absence of a device to record actual hours a patient spends in the dark, as occurred in the CLEOPATRA trial, it is only possible to look at highest mask use as an indication of probable compliance. Lower mask use patients with irregular sleep patterns may also be effectively compliant (e.g. a patient may be in the dark and sleep for 3.5 hours — if they wear the mask for the full 3.5 hours, then 3.5 hours mask use would equal 100% compliance) but to have majority of patients who sleep for

3.5 hours a night over a two year period, as it is claimed in the CLEOPATRA trial, is highly unlikely.

Furthermore, patients in the sham arm quickly realised they were not being treated and were given the option of not wearing the sham mask,[1] this suggests a violation of the intervention as described in the protocol.[15–16] Adverse event comparisons between the sham and trial arms are thus invalid, as it is not known how many patients were not wearing the sham mask or were informed that they did not have to wear it. Without the use of the sham mask there was no control of the possible interference of any background or bedroom light.

1/ Questionable Statistical Model Used for Analysis – Median Percentage

The CLEOPATRA team have chosen a median-from-baseline approach to analysing the data. While this is appropriate for monitoring the progress of the development of conditions over time, the use of this same model for analysing mask usage and compliance leads to a significant loss of information contained within the data. Unlike previous trials,[2–6] patient mask use in the CLEOPATRA trial was generally very low, presenting its own problems as here outlined in sections 3 & 4, and the combination of this low mask usage and questionable statistical model in many cases will over-estimate the actual patient compliance as the trial progresses and lose the ability to identify when patients have ceased being compliant. The CLEOPATRA approach to analysing the mask use data implies that over-compliance at an early stage in the treatment counteracts the effects of under-compliance later in the treatment, and this implication is not justified anywhere in the literature.

PolyPhotonix is in a unique position as a device supplier into the CLEOPATRA trial. PolyPhotonix own the fully anonymized usage/compliance data from the used masks that were returned for data download and have been asked by CLEOPATRA to monitor the data to track patient compliance. These data are held in the 'PPX Works' system and were used by both the CLEOPATRA management and statistical team. These data have allowed PolyPhotonix to question the validity of the analysis methods used by the authors of the CLEOPATRA study report.[1]

A crude assumption by the CLEOPATRA team of 50% of the defined compliance level misses critical data that affects the outcomes and determination. Therefore, the attempted adjustment in the protocol in reducing the compliance levels for sub-analyses to 50% and 60% is flawed. As the peer reviewers do not typically have access to the raw data, they are unlikely to have seen the percentage/number of days that the patients do not receive treatment, and only seen the presented averaged data and as such are unlikely to have had the opportunity to critically analyse the validity of the assumptions made by the CLEOPATRA team.

We do accept that some low wearer mask users (3 hours a night) might have avoided dark adaptation if this represents their normal sleep cycle, but without recorded hours in darkness vs mask use this data cannot be extracted.

The Noctura 400 records all mask usage data. After the mask is switched on, two capacitive sensors under the lighting elements can detect if the mask is being worn against the face. These data are recorded in a binary string (on-off) in two minute increments for a full 8 hours after the mask is turned on. This two-minute data resolution exists for the entire operational period of the mask (84 days). The masks also include other critical data such as the time the mask

started and was programmed, and hence data are easily parsed into a detailed log of patient use, see Figure 1.

Figure 1: An example of a mask usage data graph. The 84 days are listed down the vertical axis, and running across the horizontal axis represented by green bars is the mask usage.

'PPX Works' further allows collation of data via special reports that exports the raw data out of 'PPX Works' and gives usage data by trial site, patient and individual mask, as requested by the CLEOPATRA study team.

The authors chose a single method of analysing the dataset: looking at the median use from baseline (MFB), with considerations for masks not returned. This is the average of the cumulative mask wear up to that point divided by the potential mask wear up to that point, assuming 100% compliance to be 75% of the total potential mask wear of 8 hours per night. Hence it is possible for a patient to be up to 133% compliant if they wear the mask for the full 8 hours, every night for the entire duration of the trial. Thus, in principle, a patient who wore the mask for a full 8 hours a night could have not worn the mask at all for a quarter of the trial (six months) and still remained apparently fully compliant. While such an extreme case has not been observed, this demonstrates that a median alone represents a significant potential data loss, in which clinically relevant mask use may not be represented in the analysis. The MFB approach returns on a central tendency, rather than representing patient use throughout the trial.

An alternative method of considering average use demonstrates the flaws of a median-from baseline approach further. Alternative, more granular approaches (compliance by week or month, rolling averages analysis of numbers of missed days) are also possible. PolyPhotonix has taken a median-use-per-mask (MPM) approach in the following comparison as this

structures the average patient use over time into blocks, allowing the time progression of patient compliance to be much clearer and highlight periods where the patient was under-compliant.

The authors reported a MFB for the 155 patients wearing the light mask at every 4 months, starting at 39.5% (4th month) and decreasing down to 19.5% at month 24.
In Table 1, PolyPhotonix identified that 26 (26/155 = 17%) patients consistently met/exceeded the CLEOPATRA 70% compliance limit for the MPM approach; CLEOPATRA reported 32 patients reaching MFB.
At 24 months PolyPhotonix analysis shows only 7 (7/155 = 4.5%) patients with all masks meeting a 70% MPM; CLEOPATRA reported 24 compliant patients from baseline at 24 months.

Table 1. Median level of compliance from baseline over time based on CLEOPATRA publication[2] and percentage (number) of participants achieving and/or exceeding 70% compliance based on CLEOPATRA publication, data from a shared database[†], and their difference.

	12 months	24 months
Median based on CLEOPATRA publication[2]	25.70%	19.50%
Percentage (number) of compliant participants (≥ 70%) based on CLEOPATRA publication[2]	21% (32/155)	16% (24/155)
Percentage (number) of compliant participants (≥70%) based on data from a shared database[†]	17% (26/155)	4.5% (7/155)
Percentage (number) difference of compliant participants (≥ 70%) between CLEOPATRA publication[2] and data from a shared database[†]	4% (6/155)	11.5% (17/155)

[†]Measuring continuous use (i.e., consistently achieving and/or exceeding 70% compliance)

These discrepancies are due to the authors using the median from baseline to calculate the compliance values, hence over-compliance in one period balances non-compliance in another. Similar discrepancies can be derived for the lower compliance levels of 50% and 60%, clearly indicating that patients accounted for in the median calculation during the 4 month intervals were compliant in some months but not others. Indeed, the shared data shows usage patterns such as consistent use, declining use, erratic dips around compliance, and rarely/never used, see Figure 2. This variation is obfuscated by a median-from-baseline treatment that hides patients who have gone without treatment for substantial lengths of time.
Since shared data indicate that patients went for periods of time with no treatment but the statistical analysis as reported considers averaged wear, there is no appropriate sub-analysis of patients who met the threshold values for the entire trial period (Figure 5) or an appropriate scientifically justified number of days/periods of non-treatment. In fact, the hypothesis on which the CLEOPATRA study is based is that suppression of dark adaptation stops hypoxic conditions in the eye from developing. [7–10] It follows that retinal hypoxic conditions will develop on days that the mask is not worn and the lower compliance limits do not take this into account.

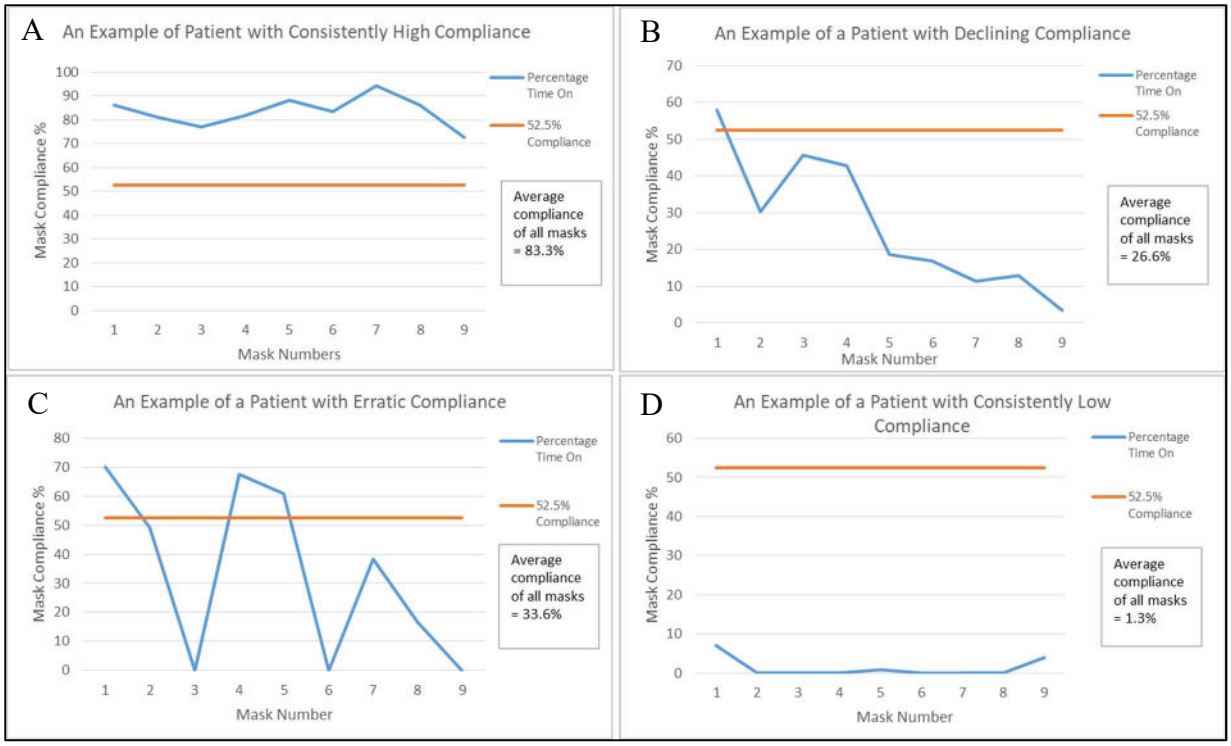

Figure 2: Examples of different modes of compliance: (A) consistent high compliance; (B) declining compliance; (C) erratic dips in compliance; and (D) rarely used compliance (any masks with 0 compliance have either not been worn at all or not returned for data download).

Mask No.	Days Not Used	Percentage Time On	Comments
1	9	70.12	
2	23	49.36	
3			Not Returned
4		67.63	
5	19	60.84	
6			Not Returned
7	38	38.47	
8	50	16.63	
9	84	0	

Figure 3: Raw data from graph C in Figure 2 – an example of a patient with erratic compliance.

For example, Figure 3 gives the raw data from behind graph C in Figure 2 (an example of a patient with erratic compliance). Each mask functions for 84 days; 2 masks have not been returned, hence 7 masks with available data x 84 days = 588 days. Of these available days there were 223 days recorded with no treatment at all, hence the masks were only worn for a total of 365 out of a possible 588 days.
From this we can conclude that extended periods during which the mask is not worn were undertaken by the patient and damage due to hypoxia may have occurred.

2/ Very low Mask Usage/Compliance

The efficacy of this intervention requires consistent correct use (compliance) for sustainable results based on the underlying hypothesis of suppressing dark adaptation.[7–10] If the mask is

not worn it follows that the hypoxia will return because the retina is still unable to meet its dark-adapted oxygen demand.

As discussed in section 2, even though the statistical model used was questionable, it is clearly evident that the overall compliance levels reached were very low as only 26 patients reached or achieved threshold in all masks used for the first 12 months. This then fell to 7 patients by month 24, see Figures 4 and 5.

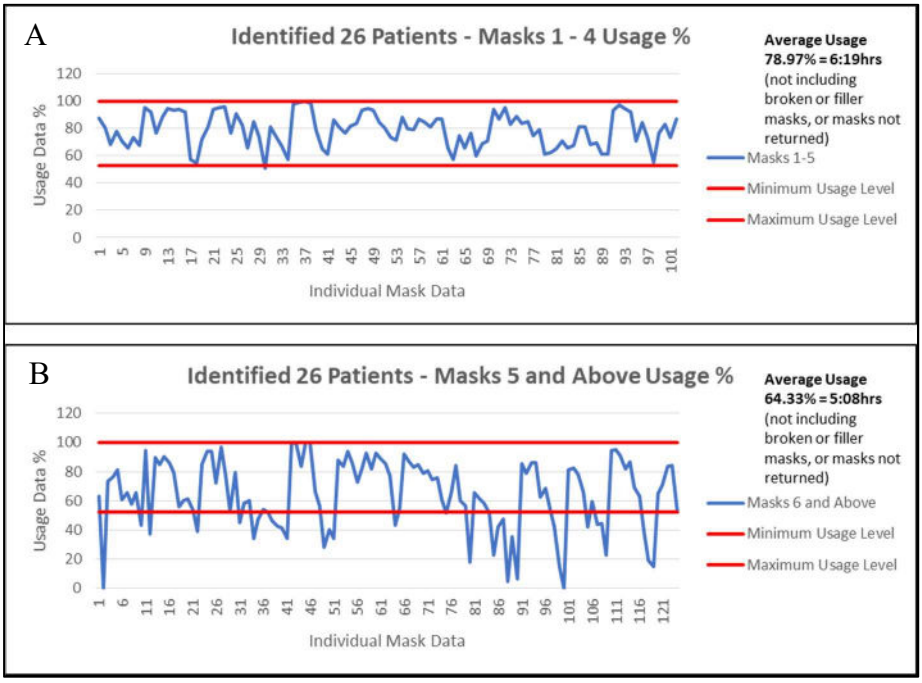

Figure 4: Graph A shows the identified 26/155 patients who achieved or exceeded the set threshold of 52.5% of 8 hours or 70% of 6 hours (CLEOPATRA tolerance) within the first 12 months. Graph B shows the same identified patients' compliance in the second year of the trial.

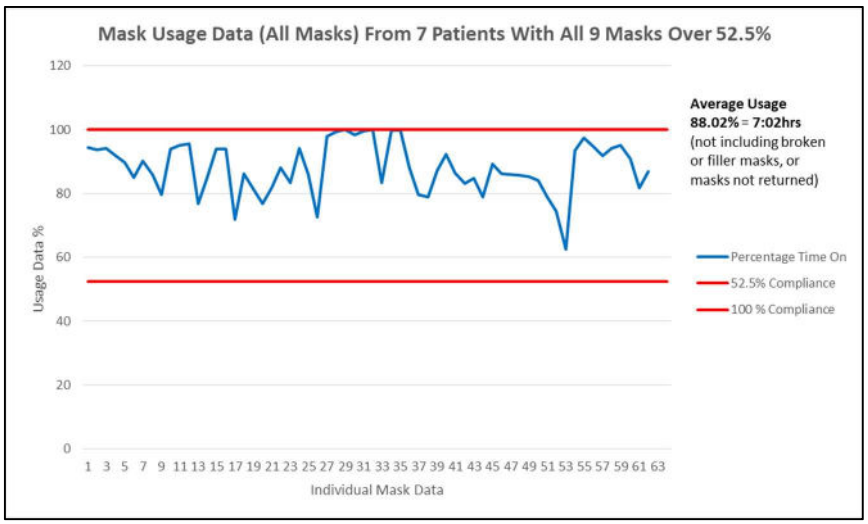

Figure 5: Identified 7/155 patients with all masks throughout the 24 month trial meeting or exceeding the set threshold of 52.5% of 8 hours or 70% of 6 hours (CLEOPATRA tolerance).

Rather than conduct sub-analysis on the identified patients who had known good compliance, the CLEOPATRA team decided to carry out sub-set analysis on lower bands of compliance at 50% of 6 hours (3 hours per night or 37.5% of 8 hours) and 60% of 6 hours (3.6 hours per night or 45% of 8 hours), see Figure 6.

If we consider the fundamental basis of light mask therapy, that the mask must be worn during hours of sleep to prevent dark adaptation, then carrying out an analysis on patients who have been far less compliant than the predetermined threshold is counter intuitive and will not yield any positive efficacy results.

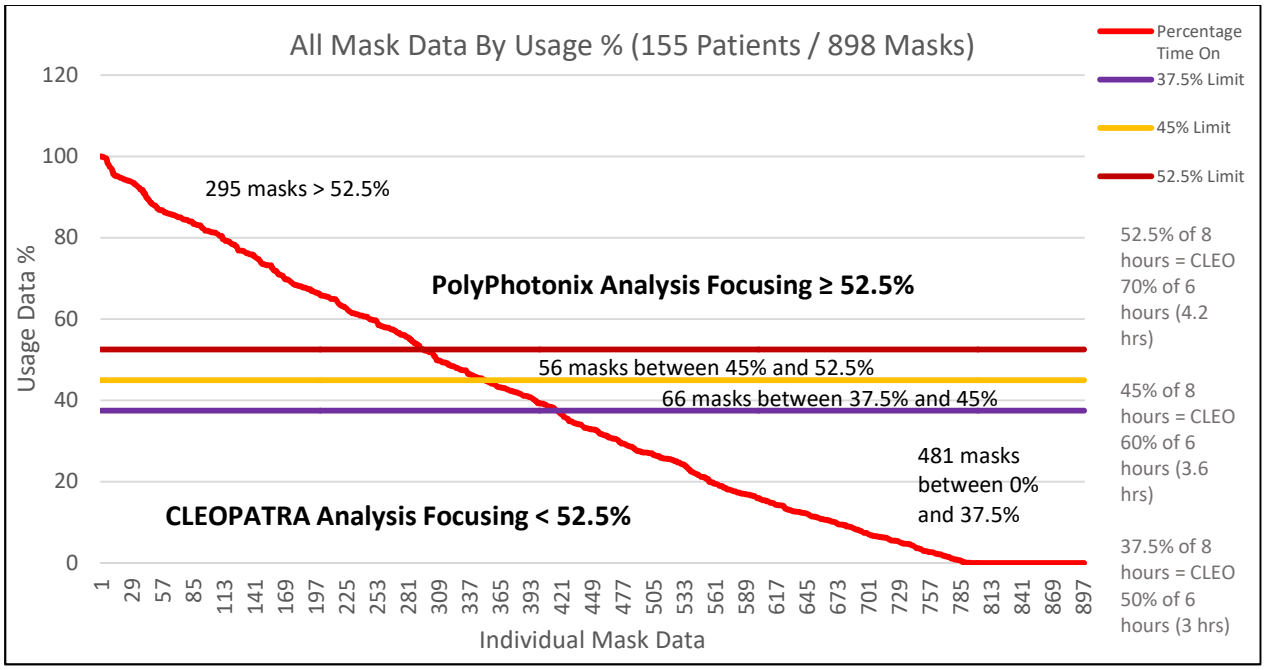

Figure 6: Usage data from all returned masks in CLEOPATRA as a percentage (excluding any broken masks or replacement masks only used for a short period until the next scheduled mask started).

3/ Patient Management Communication & Feedback Processes

Low compliance / lack of device usage is obviously of major concern. The question has to be asked why compliance has been so low in this particular study when all other studies using Noctura 400 have reported that the device is acceptable to patients.

The published paper "Safety and Acceptability of an Organic Light-emitting Diode Sleep Mask as a Potential Therapy for Retinal Disease (INSIGHT)" reported on a Noctura 400 trial over a period of 3 months.[5] On average younger healthy participants (Group A) were 56% compliant (of 8 hours) while the older healthy participants in Group B were 76% compliant over the 3 month trial period. Group C were participants with DMO and, although the publication states they had a wider variation (possibly due to sleep difficulties with comorbidities), on checking Figure 2 of the publication, the compliance average was still 5 hours per night or 62.5% of the 8 available hours.

Noctura 400 was also used in a study conducted in the Czech Republic, whose results were published in the paper: "Patients with Diabetic Eye Disease using a Potentially Therapeutic Mask. Do Sufficient Patients Wear the Mask and for How Long?".[6] The aim of this study was to assess the safety of the Noctura 400 device and whether it was acceptable to patients as a method of treatment. The conclusion was that the Noctura 400 device was worn well by the majority of patients and no major safety issues were reported.
The participants of this trial had advanced non-proliferative or early proliferative DR, so were a different cohort of patients than that of the INSIGHT study, but the average nightly wear for the trial was similar in reporting 4.96 hours or 62% compliance of the available 8 hours. The patients were also divided into groups of "good night time mask use" (over 200 hours mask wear per month = > 6.6 hours or 82.5%), "reasonable mask use" (100 to 200 hours mask ear per night = 3.3 hrs or 41.3% to 6.6 hours or 82.5%) and "questionable poor use of the mask" (under 100 hours of mask wear per month = < 3.3 hrs or 41.3%). At the end of the first month 82.9% of participants belonged to the first two groups and at the end of the 6 month trial 77.1% still remained within those two groups. This showed that the mask was tolerated well and mask wear was maintained over the 6 months.

The CLEOPATRA study was a two year trial and the authors state that the patient's median compliance decreased over the length of the study concluding the device was not suitable for long term use. The median compliance result reported in the first 4 months of the study was that of 39.5% of 6 hours, hence an average of only 2.37 hours per night.[1] This means that on average only half of the required threshold (4.2 hrs) was reached at the very start of the trial. For this first 4-month period only 48 patients (48/155 = 31%) are reported to reach the 70% threshold, the rest (107/155 = 69%) fell short of reaching threshold and fall into the 50% and 60% groups; these were sub-categories of compliance added after the start of the trial.

The CLEOPATRA study suggests that a contributor to low compliance could be that patients with non-centre involving diabetic macular oedema are asymptomatic, hence less incentivised to use the device, but as reported in INSIGHT, healthy patients had average results of 56% and 76% (of 8 hours) between the two groups (young and old).[5] These results over 3 months were much higher on healthy patients who had no medical incentive to wear the device than the CLEOPATRA reported figures at 4 months. This suggests that patient management and coaching was not at an acceptable level from the outset of the trial, hence it is virtually inevitable that compliance would only continue to decline with time as a result.

Patients' return visits within the CLEOPATRA study happened every 4 months. The Noctura 400 light-mask works for 12 weeks, then a replacement is needed. Hence at every visit the patient was to return any used/completed masks for data download. Unfortunately, out of a total number of 1096 programmed masks that were handed out to patients 157 (14%) did not have the data downloaded. The likely assumptions are that either the masks were not returned by the patients or the mask data had not been downloaded by the site. Whatever the cause, this means that 14% of all possible compliance data was missing from the analysis. The source data also clearly show numerous patients where multiple masks were continually handed out for use even though previous used ones had not been returned for data download, in some occasions over 12 months of use. This suggests poor communication between the trial site and the patients.

Additional methods of patient encouragement were proposed by PolyPhotonix before the study started such as the direct feedback of mask compliance data to patients at the time of data download, as similar feedback in other studies has demonstrated improved usage.[17] This

method is used by the commercial customers supplying Noctura 400 with their patients and has proven successful. These suggestions were not employed by the CLEOPATRA team and patients returning their masks were never shown their usage/compliance data. The study nurse was also not able to access this information and had to rely on the trial manager picking up on any low patient compliance. This was then fed back to the trial nurse, who then had to remember to mention to the patient about their low compliance at their next visit, which could be anywhere up to 4 months in the future. This method of feedback is complicated, has obvious delays and is open to misprocesses. Mask wear monitoring is a crucial part of Noctura design, thus the Cleopatra policy of not sharing the mask wear data with the patients is clear evidence of inappropriate evaluation of this device.

A further example of concerns raised by PolyPhotonix to the CLEOPATRA trial manager came after the Principle Investigator of William Harvey hospital asked PolyPhotonix in detail how does the device work (turning the device on) 12 months into the trial. This means the patients were unlikely to be instructed on correct and compliant use.

PolyPhotonix has been supplying Noctura 400 commercially for a number of years now and our customers (Ophthalmologists/Optometrists) are coached on how best to manage the patients using Noctura 400. This includes sharing compliance data from returned masks with the patients helping to keep them focused and engaged with the treatment, and carrying out mentoring should the compliance be low. Regular phone calls to the patients to provide support through the first few weeks of use has also proved critical through this period of adaption and habit change in wearing something new during sleep and is proven to yield good compliance outcomes long-term.

PolyPhotonix has carried out analysis on their commercial data to compare with the results reported by the CLEOPATRA study. As can be seen in Figure 7, on checking all of the returned masks from commercial use the percentage of masks with a compliance level ≥ 52.5% (which is equal to the 70% threshold in CLEOPATRA study) is 79.8%, while all returned masks in the CLEOPATRA study ≥ 52.5% threshold is 32.9%.

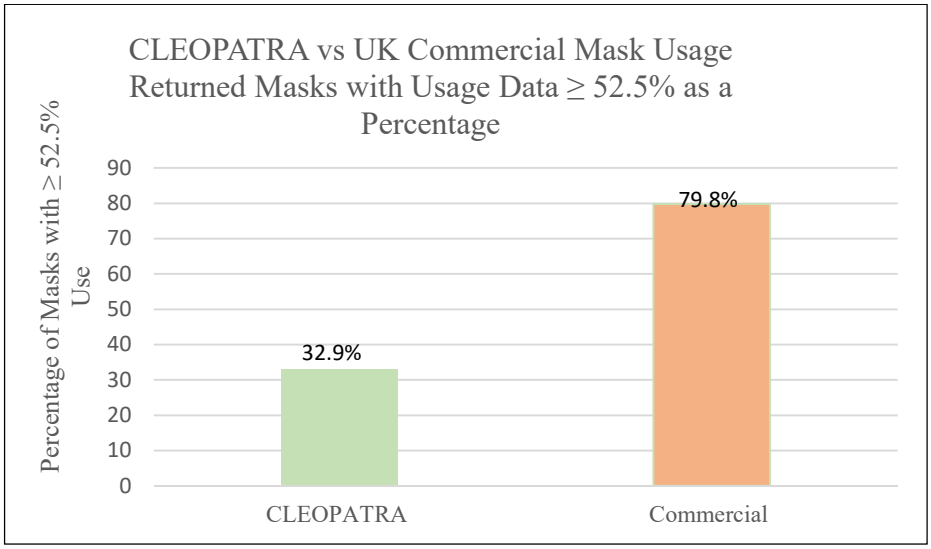

Figure 7: Comparison between all returned masks from CLEOPATRA study and PolyPhotonix commercial activity. Percentage of masks with compliance data above 52.5% (which is equal to the CLEOPATRA 70% threshold of 4.2 out of 6 hrs per night)

4/ Questionable Interpretation of 12 Month Diffuse DMO Benefit which was Unsustained at 24 Months

CLEOPATRA states that the light-masks significantly reduced diffuse DMO at 12 months, but this effect was not sustained at 24 months, concluding that the effect was transient and minimal. This was interpreted as a loss of efficacy of the intervention but the analysis does not take into account the previously discussed drop in compliance in the second year, potentially explaining the transient nature of the effect.

Therefore, deriving the conclusion that the device "did not confer long-term therapeutic benefits" when patients were not treated as intended is a study limitation.

Conclusion

The CLEOPATRA study confirms Noctura 400 safety and patient benefit at 12 months. We welcome further post-hoc analysis, where an appropriate statistical model is used to analyse the effect of mask usage patterns. Contrary to authors' views, we feel that better designed and monitored studies will be able to demonstrate the prolonged efficacy of this device in Diabetic Retinopathy.

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