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A Novel Drug-Eluting Indwelling Pleural Catheter for the Management of Malignant Effusions

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To the Editor,

Malignant pleural effusions (MPE) affect an estimated 150,000 people per year in the US.(1) Average life expectancy following diagnosis is 4-6 months.(2) Management usually involves either insertion of an indwelling pleural catheter (IPC) or talc pleurodesis. Talc treatment typically requires a hospital stay of at least four days,(3) but IPCs allow ambulatory management and can be inserted as a day case. IPCs, however, induce pleurodesis less effectively, with success rates of approximately 45% (compared to 70% for talc) at a median of 52 days.(4)

A new drug-eluting IPC has recently been developed, with the aim of enhancing effectiveness by the addition of an established pleurodesis agent, silver nitrate, as a slow-release coating. The total dose delivered (100mg) is considerably lower than has historically been given during bolus administration. The SEAL-MPE study (NCT02227732, REC 13/WA/0379 and MHRA 2014/011/028/081/010) was a first-in-human trial designed to evaluate the basic safety profile of the novel silver nitrate-coated indwelling pleural catheter (SNCIPC) device in MPE. All patients documented informed consent and a safety data committee met at frequent intervals. Some of the results of this study have been previously reported in the form of an abstract.(5)

The protocol and analysis plan were designed jointly by the investigators and the Sponsor. A prospective, unblinded, single-arm cohort design was used. Patients were recruited consecutively from Southmead Hospital (Bristol, UK) between July 2014 and May 2015. The full trial follow-up period was 60 days, with a target of ten evaluable patients. The primary objective was to describe the number and nature of adverse events (AE), defined as any untoward occurrence in a participant during the trial period. AEs were further classified as

being expected/unexpected, mild/moderate/severe and trial/disease/device related. A standard definition of a serious adverse event (SAE) was used.(6) Secondary objectives included assessments of pleurodesis success, patient symptoms, silver levels and inflammatory markers. Patients were eligible if they had a recurrent pleural effusion caused by proven malignancy with clinical evidence of adequately expandable lung following thoracentesis.

The SNCIPC was inserted under local anaesthetic. Drainage took place daily until day 14 post-insertion, with a reduced frequency thereafter. Patients were defined as having undergone successful pleurodesis once they drained ≤50mls of fluid on three consecutive occasions over a minimum of five days.

All patients who were consented were included in the analysis. All trial data were available to the investigators and were analysed using IBM SPSS v23 (IBM Corp., Armonk, NY, USA) and Prism v6 (GraphPad Software, La Jolla, CA, USA). The mean age of participants was 70·3 years (SD 11·09) with 5/10 male. They had undergone a median of 1.5 (range 1-3) therapeutic pleural procedures in the previous three months. Four patients were on anti-cancer therapy, but all had developed their effusion whilst on treatment.

A total of 69 AEs were recorded during the trial period. The majority (42/69) were related to underlying conditions and 17/69 were device-related. There were no unexpected adverse device events (UADE) recorded. Eight events were documented as serious (6/8 post-insertion). Only one SAE was related to the trial device: chest pain requiring increased analgesia, extended stay, and ultimately device removal (figure 1).

After excluding one patient in whom non-expandable lung was only revealed after catheter placement, 8/9 (89%) patients met the criteria for pleurodesis during the study. The median time to pleurodesis was 4 days (IQR 2-6) (figure 2). All patients who achieved pleurodesis maintained this effect at day 28 and 60 follow-up visits.

Patients complained of minimal chest pain at baseline, with a median VAS score of 1.5mm (0-4.0). This rose on day one post device insertion to a median of 36.0mm (14.0-65.0) before reducing to 4.0mm (0-18.0) in day seven.

No deleterious increase in either blood or pleural fluid silver levels was identified, with peak median blood values noted on days 14 and 28 respectively. The peak median value for blood C-Reactive Protein (CRP) 103.5mg/L (56.0-142.0) was seen on day seven.

Given the short average life expectancy of those with MPE, it is vital to minimise the impact of effusions on quality of life. Some authors have attempted to use a normal IPC as a delivery method for a chemical agent, although this approach can mandate relatively frequent outpatient visits.(7) The SNCIPC tested in our study, however, is the first device which has attempted to truly be a complete solution. Indeed, although the general concept of drug-eluting devices is well-established, especially in coronary artery disease,(8) the SNCIPC is the first drug-eluting device designed for intrapleural use.

The relatively high number of recorded AEs was anticipated given the stringency of event recording and the palliative nature of the recruitment population. The SNCIPC nonetheless appeared to be well-tolerated, with 15/17 device-related AEs classed as mild. No cases of pneumonia were attributable to the device. One patient required the SNCIPC to be removed due to early pain, however pain is a common and expected side effect of both pleurodesis

and IPC insertion and can usually be controlled with simple analgesia. Indeed, a degree of patient discomfort would actually support the notion of the SNCIPC causing the desired inflammatory stimulus to cause pleurodesis.

Of the nine patients with expandable lung, 89% achieved pleurodesis after a median of four days, which compares favourably with talc and is far superior to what might be expected with an IPC alone, even with aggressive drainage regimens or more rigorous patient selection.(9, 10)

Due to the small number of patients involved, no firm conclusions can be drawn about the SNCIPC's efficacy from our study. Furthermore, SEAL-MPE was undertaken in a specialist centre with significant pleural and clinical trial expertise available, with the frequency of drainage and review perhaps not easily translatable to routine practice.

Nonetheless, the SNCIPC has the potential to represent the most important advance in the management of recurrent MPE since the original PleurX catheter was introduced two decades ago. The results of this study have subsequently led to an ongoing multicentre, international, randomised controlled trial which will look to more comprehensively investigate the efficacy of the SNCIPC device.

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Figure 1 – Summary of primary outcome (adverse events)

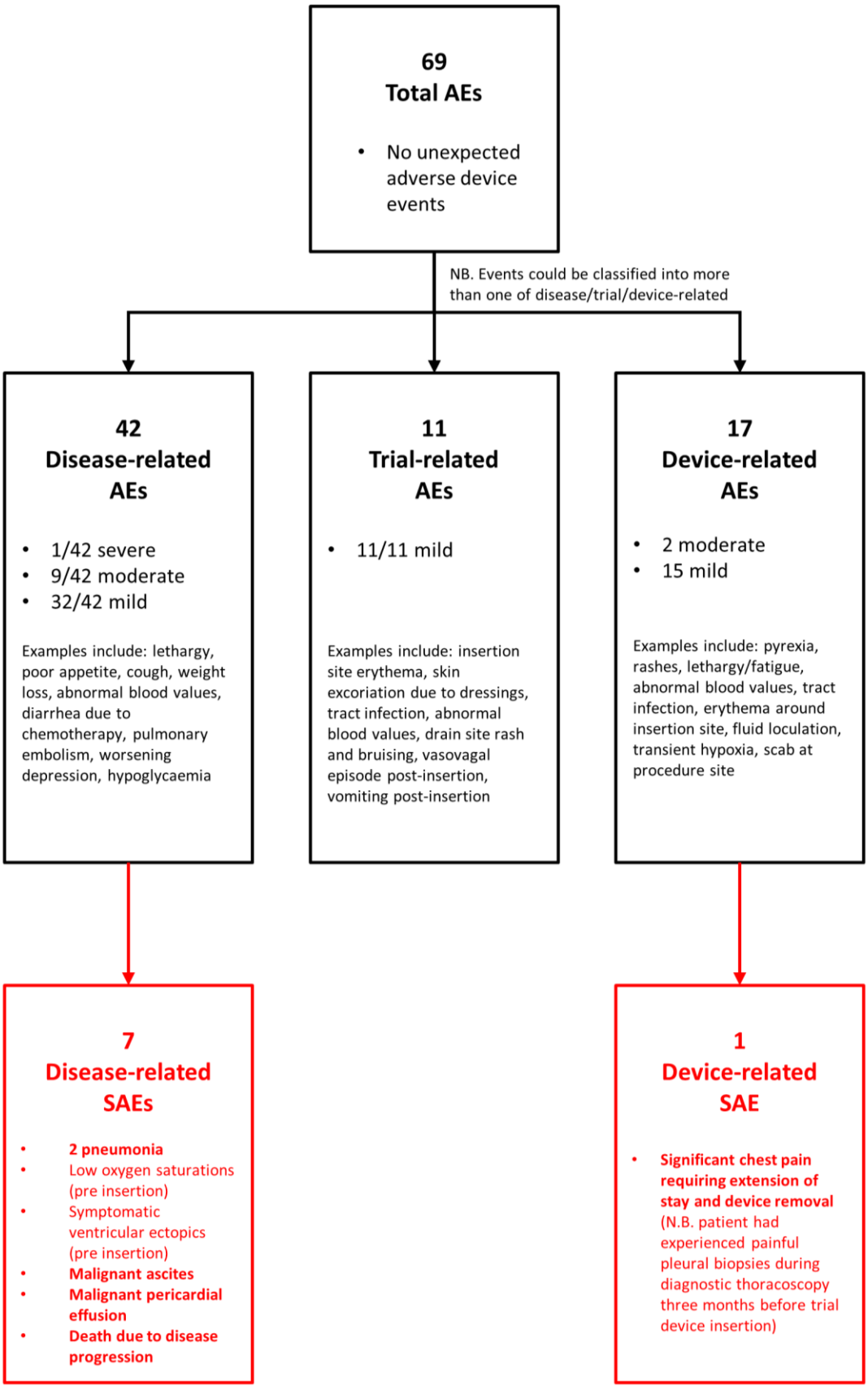

FIGURE 1 LEGEND: AE = Adverse Event (any untoward occurrence in a trial participant); SAE = Serious Adverse Event (any adverse event leading to death; which is life-threatening; leading to hospital admission or extension of hospital stay; causing persistent disability or incapacity)

Figure 2 – Kaplan-Meier survival curve of pleurodesis success in all ten trial patients

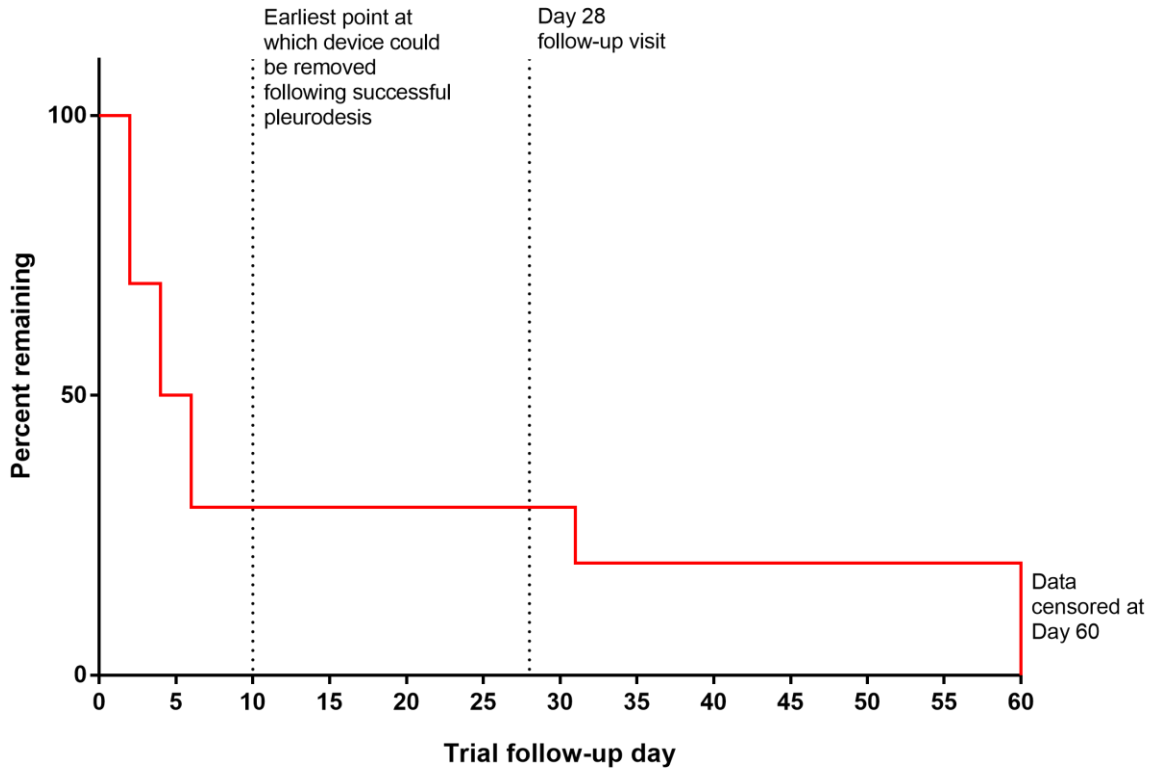

FIGURE 2 LEGEND: The majority of participants achieved the pre-defined pleurodesis criteria at a median of 4 days. The study was designed such that catheters could not be removed before day 10 post-insertion unless felt to be clinically indicated by the Chief Investigator.