Author’s response to reviews

Title: A novel endothelial damage inhibitor for the treatment of vascular conduits in coronary artery bypass grafting: protocol and rationale for the European, multicentre, prospective, observational DuraGraft registry

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Response to Reviewers:

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A novel endothelial damage inhibitor for the treatment of vascular conduits in coronary artery bypass grafting: protocol and rationale for the European, multicentre, prospective, observational DuraGraft registry

We thank the editor and reviewers for their valuable comments to improve the manuscript. We respond in a point-by-point fashion:
RESPONSE TO REVIEWER #1

Reviewer #1:

This is the study protocol for a prospective non-randomised multi-centre registry looking at the effects of DuraGraft solution on the outcomes of saphenous vein graft and free arterial grafts for patients undergoing isolated or concomitant coronary artery bypass grafting. This registry is being undertaken in parallel with a randomised controlled trial of the solution that will be used to corroborate the findings of a previous observational study.

1) The protocol is well written with excellent English throughout. There are a few typographic errors such as "neurological deficient" rather than "neurological deficit" in Table 1 and the unclosed bracket on line 49, page 7 which would be attended to in proofreading. Having said this, I would favour a more judicious use of parentheses to describe examples and exceptions throughout the paper, although this is a stylistic opinion only.

Response: Typographic errors have been corrected in the revised manuscript accordingly.

I have several comments about the protocol as it is presented:

2) p7,L58 - The registry has already begun collecting data and, as such, it would seem to be redundant to publish the study protocol nearly 3 years after it had begun.

Response: We thank the reviewer for this remark. We however respectfully disagree with this statement for the following reasons: The registry has been designed with a follow-up period of up to 5 years with first outcomes planned for publication after completion of the 1-year follow-up for the entire cohort and the main results to be published when the 5-year follow-up is complete. Considering that the enrolment as well as the initial data cleaning and validation is anticipated to be completed towards the end of 2019, the 1-year outcome data are expected to be complete and analyzed by end of 2020 with anticipated publication in 2021. Analogous to this schedule, publication of the 5-year data will only occur in 2025. Moreover, sub-studies are likely to even be published after that period. We have mentioned this planned timeline in the revised manuscript accordingly. Therefore and when considering this long timeline ahead before the first data will become available, we do not see any redundancy in publishing the protocol at all. We believe that publishing the protocol is important and it will substantially contribute to make the surgical society aware about this multi-European registry effort. In addition, it is important to recognize that the Journal of Cardiothoracic Surgery specifically invites the submission and publication of protocols of planned or already running studies. Please see the author’s guidelines accordingly (https://cardiothoracicsurgery.biomedcentral.com/submission-guidelines) and in fact, this is one of the reasons why we have selected the Journal of Cardiothoracic Surgery for the submission of our work.
3) p8,L38 - Which version of EuroSCORE?
Response: It is the EuroSCORE II. The revised manuscript has been updated accordingly.

4) p9,L20 - presumably the outcomes are both composite outcomes only?
Response: Yes, it is correct, that MACE and MACCE are composite primary and secondary outcomes, respectively. However, we will also report single outcomes for mortality, non-fatal myocardial infarction, repeat revascularization and stroke.

5) The overall premise of the registry itself - to establish practices in CABG and define current multinational outcomes and methodologies is laudable. How that information will be utilized is less clear:
Response: The primary and secondary endpoints will consider all centers with various harvesting and grafting techniques and therefore the registry will serve as a strong resource for real-world CABG data from all around Europe.

In brief, the registry is designed with a follow-up period of up to 5 years with first outcomes planned for publication after completion of the 1-year follow-up for the entire cohort and the main results to be published when the 5-year follow-up is complete. Moreover, sub-studies are likely to even be published after that period.

6) if the registry shows a narrow confidence interval for the composite outcomes, in the absence of patency information, this may lead to the question about the sensitivity of the surrogate outcome measures. If, as I would guess, the confidence intervals are wide and there is evidence of variation between centres, correlating this with the results of the randomised controlled trial will be difficult and the temptation to undertake underpowered subgroup analyses will be great.
Response:
We agree with the reviewer, that comparing the CT-imaging based RCT (NCT02272582 and NCT02774824) to the registry is difficult. However, such a direct comparison is also not intended, especially as the RCT primarily focuses on early graft remodeling parameters (i.e. wall thickness) as a measure for intimal hyperplasia (as a measure for graft disease), while the registry reports clinical outcomes after DuraGraft treatment. Nevertheless, and as mentioned in our discussion section, it is important to recognize, both studies represent valuable resources when implementing and validating such new devices or treatments in clinical routine. Instead, and in
order to compare clinical outcomes, a potential patient-level matched comparison to another large-scale registry from published literature is being pursued.

7) Although I agree that best practice is to publish protocols for studies, I do not know that the present submission adds enough to the existing protocol description on the trials website to warrant separate publication. However, the content - and the results of the registry - would be of interest to the readers of the journal who may not otherwise be aware of the study and this would be the main reason to consider publication if the editors saw fit.

Response: As the reviewer correctly states, publishing of study protocols represents an important part in clinical research and has become a standard practice nowadays. The content of our protocol in this manuscript significantly exceeds the information provided on the clinicaltrials.gov website and therefore represents a valuable contribution for the surgical society. The intention of publishing this manuscript is manifold: 1.) to provide a detailed overview of this large-scale registry effort, but more importantly, 2.) to raise the overall awareness in the cardiosurgical community to the subject of vein graft disease and failure, which still represents one of the largest problems in our daily CABG routine, especially when considering that more than 80% of CABG procedures are performed with SVGs. Please also see our detailed response to comment 2 above in this regard.

RESPONSE TO REVIEWER #2

1) Dear authors,

Thank you for submitting the study manuscript and the opportunity to read it critically. From a personal perspective, publishing a study protocol only makes sense if reviewers and journal readers can participate in a discussion about the study design. In your case, patient recruitment is completed, and the data is about to be evaluated. In this situation, it makes no sense for me to publish a protocol.

Response: We respectfully disagree with the reviewers’ statement. In general, publishing study protocols is not primarily intended to redesign study protocols, it is intended to inform the cardiosurgical community about such ongoing large-scale clinical efforts and to raise awareness on ongoing and upcoming studies. This is why the Journal of Cardiothoracic Surgery specifically invites the submission and publication of protocols of planned or already running studies. Please see the author’s guidelines accordingly: (https://cardiothoracicsurgery.biomedcentral.com/submission-guidelines).

Moreover, and as mentioned above (please also see above our detailed response 2 to reviewer 1 in this regard) the registry was planned with a follow-up period of up to 5 years with first
outcomes planned for publication after 1-year FU completion of the entire cohort and publication of the main results 5-year FU is complete. Considering that the enrolment and initial data cleaning (and validation) is planned to be complete by the end of 2019, the 1-year outcome data will only become available by end of 2020 thus enable publication only in 2021. Analogous to this schedule, publication of the 5-year data will be possible in 2025. Therefore, considering this long timeline ahead before the first data will become available, we do not see any redundancy in publishing the protocol at this point and rather deem it an important tool to make the surgical society aware about this multi-European registry effort. We have mentioned this planned timeline in the revised manuscript accordingly.

To the content points:

2)

You rightly point out that in addition to RCT studies, studies from the health services research also have their place. In this case, however, it is a relatively new medical device (Duracare) that did not have to show in its approval process that it is also efficient. The approval is only from the point of view of safety. Especially at the present time is a large-scale randomized, blinded (!?!?) study, the only way to show evidence. You designed a study, with the same pitfalls that has often been made in cardiac surgery (e.g., OPCAB, robotic surgery etc ...): the registry data are highly selected and do not show the true functioning of new therapies or medicine products.

Response: We respectfully disagree with the reviewers’ statement that registry data is highly selective and do not show the true functioning of new therapies. Although RCTs are considered to be a prerequisite to establish the risk–benefit ratio for medical therapy, these trials have several inherent limitations. For example, strict inclusion criteria applied in RCTs exclude many patients in a real-world setting. Extrapolation of procedural outcomes observed in such RCTs to other centres with different experiences might be difficult in RCTs as well. To overcome these limitations and reflect a real-world setting, large-scale, well-designed observational registries with long-term follow-up are crucial as a complement to RCTs. In addition, initial data from the randomized multicenter trial using longitudinal MDCT angiography analysis as well as data from a large retrospective analysis with 2436 patients and a mean-FU of 8.5 years provided first promising efficacy results1, 2.

3)

Further discussion points on the protocol make little sense in an affiliated study, but I would like to list it in a nutshell:

Why n = 3000 patients?

Response: The large size of n=3000 patients has been selected for several reasons: 1.) to enable the participation of multiple European countries comprising of academic and non-academic small-, mid- and large-scale sites thereby reflecting European real-world CABG data; 2.) to
achieve enough outcome data taking into account patient drop outs and missing data over the long course of 5-year follow up; 3.) to enable subgroup analyses within the registry but also against other CABG registries.

4)

Study is not independent! Sponsor Somahlution. Real world data must be independent.

Response: We respectfully disagree with this statement. It is correct that Somahlution sponsored this registry. However, the registry is carried out completely independent by the PIs and an independent clinical events committee has been set up for adjudication of adverse events which meet protocol defined outcomes/endpoints over the course of the study (please see our study design section).

Furthermore, it is important to recognize, that the solution is not reimbursed by insurances, and therefore sponsoring is necessary to undertake a study of this size. In general, it is also to highlight that sponsoring does not necessarily mean dependency. In fact, the majority of large RCTs and registries are nowadays supported by the industry and don’t make them less independent. Moreover, the registry is overseen and directed by an independent scientific advisory committee comprising 10 members from the various study sites and regions.

5)

Recruitment: 2700 patients in 38 centers in 2.5 years = every 10 days a patient inclusion: why is the number so low.

Response: We thank the reviewer for this calculation. However, it is important to recognize, that not all sites started enrolling at the same time for logistical and regulatory reasons (i.e. IRB and ethics approval, country-specific site set up, etc.) Not all sites started at the same time. After initiating the registry at the majority of sites, a mean enrollment rate of 100-150 patients per month was achieved.

6)

No protocol specifications for the type of graft storage in DuraGraft, duration of storage, definition of the rinsing processes, details of who has taken the grafts, etc

Response: We principally agree with the reviewer that a "standard procedure" or a "best practice" would be desirable. However, this is challenging to implement in such a large scale study and in addition, the intention of this study was to interfere with the clinical routine as less as possible. Therefore, the only requirement was to flush or store free grafts in the solution. Due to expected high variability within procedures and centers (or even surgeons), harvesting protocol was left to the discretion of the operator. In this context, we would like to draw your attention on our recent review article in Nature Reviews Cardiology emphasizing on best practices of the use of saphenous vein grafts in contemporary CABG surgery4.
Especially for reasons that are mentioned in my introduction, I recommend a rejection of the manuscript.

Response:

Again, we respectfully disagree with this statement and would like to refer the reviewer to our detailed response above regarding the general concern of publishing study protocols.

RESPONSE TO REVIEWER #3

Authors present the study design of the DuraGraft registry: this is a prospective, multicentre, non-randomised observational study registry that will assess the potential benefit of DuraGraft to efficiently protect against the development and progression of VGD or VGF in patients undergoing CABG procedures. The objectives of this registry include the long-term assessment of clinical outcomes, including major adverse cardiac events (myocardial infarction, death, repeat revascularisation), quality-of-life data, and health-economic outcomes in patients requiring CABG procedures and whose vascular grafts are treated with DuraGraft. The topic of the investigation is very interesting and the study is well designed. I have only some considerations:

Response: We would like to thank the reviewer for this very supportive comment.

1) - authors have declared in the "Discussion" Section that parallel to this registry, a prospective, randomised trial is underway in patients undergoing isolated CABG with at least two SVGs, which will specifically evaluate the graft remodelling using sequential multidetector computed tomography angiography; however I ask them to discuss why the study of graft patency using coronary angiography or CT-scan was not considered as an end-point of this study;

Response: We agree with reviewer that this would have been desirable. However, a large-scale study with MDCT angiography would have gone logistically and financially beyond the scope of this registry, which mainly focused on clinical outcomes.

2) - another outcome that authors have not considered is the angina symptom; although quality of life was evaluated with the EQ-5D-5L, this instrument comprises a question about pain, but not specifically investigate the recurrence of angina. Please comment on it.

Response: We agree with the reviewers’ concern. Recurrence of angina symptoms is being obtained as part of the follow-up but we have not considered this as part of primary and
secondary outcomes. However, recurrence of angina will be reported separately.

RESPONSE TO REVIEWER #4

Caliskan et al. are ongoing multicentre, prospective observational registry which enrol 3000 patients undergoing an isolated CABG procedure or a combined with at least one saphenous vein grafts or one free arterial graft. Data on baseline, clinical, and angiographic characteristics as well as procedural and clinical events will be collected. They set primary outcome measure as the occurrence of MACE. Secondary outcome measures are the occurrence of MACCE. Events will be adjudicated by an independent clinical events committee. Finally, clinical outcome associated with DuraGraft will be examined.

They mention that this European, multi-institutional registry will provide detailed insights into clinical outcome associated with the use of DuraGraft. Beyond that, and given the comprehensive data sets comprising of patient, procedural, and graft parameters that are being collected, the registry will enable for multiple subgroup analyses targeting focus groups or specific clinical questions. These may include analysis of subpopulations such as patients with diabetes or multimorbid high-risk patients (patient level), evaluation of relevance of harvesting technique including endoscopic versus open conduit harvesting (procedural level), or particular graft-specific aspects (conduit level).

I read the protocol with interest.

1) However, the study design seems to be too rough. To evaluate the drug effect on the graft patency and effect on prevention of stenosis, 3D-CT or CAG are mandatory. MACE or MACCE does not represent DuraGraft effect directly. The patency of bypass grafts depends on not only on the graft preservation technique but also many other factors, including the runn off, proximal anastomosis device, distal anastomoses, quality of the graft, its length, and the compatibility of the diameter of the coronary artery and graft. Recently, some groups published superiority of no-touch SVGs with fat tissue. SVGs were neither stripped nor distended and exhibited a higher patency comparable to that of LITA. Among these many factors affect graft patency, I wonder how much DuraGraft short tome preservation contribute to elevate the graft patency.

Response: We thank the reviewer for this important remark, but respectfully disagree with the statement that MACE or MACCE does not represent DuraGraft effect directly. As previously reported by Haime et al., intraoperative treatment with DuraGraft was associated with a lower risk of long-term adverse events in treated patients. (Please also see our Response 1 to comments of Reviewer #3 on discussion of MDCT angiography). Of note, although no-touch pedicled vein harvesting was described earlier with superior patency outcomes, results from the recent randomized controlled SUPERIOR SVG trial did not demonstrate superiority of the no-touch saphenous vein harvesting technique on graft patency or clinical outcomes after CABG surgery compared with conventional harvesting3.
In this context, we would like to draw your attention on our recent review article in Nature Reviews Cardiology discussing best practices of the use of saphenous vein grafts in contemporary CABG surgery4.

2) In contrast, similar study protocol using Dura Graft (NCT02272582/NCT02774824) reported by Ali et al. assess MD-CT angiography at 4-6 weeks, 3 months and 12 months. In their study, the primary short-term endpoint is the magnitude of change between 4-6 weeks and 3 months post-CABG surgery in mean wall thickness between the paired grafts as determined by 64-slice or better MDCT angiography. The wall thickness will be calculated every 10 mm for all grafts (varying lengths of the grafts and thus number of measurements used in creating the average for each graft) by subtracting the lumen diameter in millimetre using contrast enhanced CT from the total vessel diameter in millimetre using non-enhanced CT and dividing by two. Each 10 mm segment is graded for quality, and the mean wall thickness for the whole graft will be computed as the average of all wall thickness measures of acceptable quality for each of the study grafts at 4-6 weeks and 3 months. The magnitude of change will be calculated per graft as the difference between the 4-6 weeks and the 3-month time points. The magnitude of these changes will then be compared between the paired grafts. The primary long-term endpoint will be the change from 4-6 weeks to 12 months following CABG surgery in lumen diameter calculated as the average of the mean lumen diameter over each graft and the lumen diameter at point of maximal stenosis within graft, using 64-slice or better MDCT angiography. Compared to their protocol, MACE and MACCE as an endpoints, study message will be weak.

Response: We thank the reviewer for this comment. The aforementioned MDCT study focuses on early graft remodeling parameters as a measure for intimal hyperplasia (as a measure for graft disease) and will provide longitudinal insight on changes of wall thickness, lumen diameter and others and its potential impact on graft patency. However, this study is not powered for clinical outcome and in particular, it is important to recognize that reduced patency (or graft occlusion) of SVGs don’t necessarily always translate into clinical events and many patients even stay asymptomatic. This again highlights the general question whether and to what extend such remodeling parameters and graft stenosis / occlusion can be used as a surrogate marker for the risk and occurrence of clinical adverse events. In the light of this aspect, data obtained from a study, which solely focuses on clinical outcomes, will always be valuable to validate such morphological or patency studies as well as general pathophysiological hypotheses on graft disease and failure.

References

