

FIRST TRINAM® EXPERT WORKSHOP

Synopsis

Chair:

Higham, Paul Director of Commercial Development, Ark Therapeutics Group plc

Attendees:

Davenport, Andrew	Consultant Nephrologist/Honorary Senior Lecturer, Royal Free Hospital, London
Davidson, Ingemar. J	Professor of Surgery, UT Southwestern Medical Centre, Dallas, USA
Eckland, David	Director of Research and Development, Ark Therapeutics Group plc
Lawson, Jeffery	Associate Professor of Surgery, Duke University Medical Centre, NC, USA
Schild, A. Frederick	Professor of Clinical and Vascular Access Surgery, University of Miami, USA
Schroeder, Torben. V	Professor of Vascular Surgery, University of Copenhagen, Denmark
Szczzech, Lynda	Director of Nephrology Research, Duke University Medical Centre, NC, USA
Work, Jack	Professor of Medicine, Dialysis Access Centre of Atlanta, USA

1. Pre-Clinical and Clinical Development

Collar

- The use of the collagen collar and its associated application in the Operating Room (OR) was discussed.
- Comments from investigators involved in the phase II study highlighted some issues with removing the collar from the mandrel and issues surrounding the placement of the collar around the anastomosis. The experts present with experience of the recently developed improved collar commented that it performed much better than the first version when used in recent pig studies. The issue of end-to-side anastomoses had been solved by the new prototype design, which included a hole in the top of the collar to accommodate insertion of the graft.
- It was pointed out that Ark needs to be careful that the equipment used to warm the collagen glue for both the phase III study and subsequent commercialisation must be easy to use and function properly. The surgeons involved in the phase II study suggested that there was a training element required to being able to use Trinam, but this was not very significant and should be easily accommodated into an initial training programme at the time of commercialisation.
- It was noted that it is obvious when the collar is not fitted correctly, and that to insert the needle appropriately is not difficult. However, the usual concern about more widespread use post-approval was raised and Ark should be aware that whatever they could do to minimise the risk of misplaced application or stick injuries should be considered as phase III development progresses. "There is a learning curve to this but it's a short learning curve."
- Discussion was held as to whether the collagen glue is the most appropriate sealant to use and it was generally agreed that this is appropriate as it fits with the overall biodegradable collagen theme.
- The ability to do end-to-side anastomosis was felt to be a significant positive step forward allowing easier surgery and allowing many more patients to be included as part of the study recruitment for phase III.
- A summary of the phase II safety study results was presented and the overall reaction of the group was that the study had demonstrated Trinam to be safe in the patient population studied. The collagen collar had effectively limited biodistribution.
- It was harder to draw firm conclusions from the patency data. Although these were positive it was in a small number of patients and so it is appropriate to move forward into a larger phase III study, where patency can be definitively determined.
- Discussion centred around the usefulness of VEGF in the setting and whether a relatively short-lived effect was able to have an impact on long-term patency. It was felt that the hypothesis of limiting vascular injury and improving the early healing response to improve long-term outcome was appropriate and the Phase III study would be designed with this hypothesis in mind.

- The group was able to clarify the sometimes confusing definitions of primary patency, primary assisted patency and secondary and overall patency. Ark described that the primary endpoint of the phase III study would be to look at overall graft survival. Subsequent discussion raised the question of whether primary patency would not be a more appropriate endpoint and the overall conclusion was that the secondary overall patency was the least subjective measure and the one most clearly linked with patient benefit. For these reasons this is the primary endpoint suggested by Ark and agreed with the FDA as the appropriate endpoint for the phase III study.
- Further discussion on the design of the phase III study centred around the fact that the study would be open label in that the surgeon would not apply a graft or a dummy solution in the control arm. The control arm was suggested as such because it is unknown in man if the collar alone could exert a treatment effect (although no collar-alone treatment effect has been evident in the animal studies conducted) and would therefore not be a true placebo. From this, the issue of potential investigator bias was raised and discussed. Ark pointed out that the patients would be randomised in the OR to eliminate investigator bias in patient selection and that through Special Protocol Assessment Ark and the FDA will agree a protocol that would minimise potential investigator bias going forward.

2. Vascular Access Trends

- The current trends in vascular access were presented along with the KDOQI/CMS targets for prevalence of fistulae.
- In summary, the group felt that the KDOQI/CMS target of 66% prevalence of fistulae by 2009 was unlikely to be achieved and furthermore Ark's projection of 55% may also not be achieved by that time. The main reasons for this are that it is felt fistulae may already be being used inappropriately in some patients who would derive greater benefit from a graft and early movement away from catheter.

"I don't think fistula prevalence will get near the levels seen in other cultures or countries. Surgeons have too quiet a voice regarding KDOQI guidelines.... For instance, it may be much more appropriate to put an elderly patient on a graft and get them off the catheter."

In addition, the US population is different from Asia or Europe in that there is a higher prevalence of obese and diabetic patients and that in the future there is expected to be a large elderly population in whom fistulae are both more difficult to place and are less likely to mature.

- There was general agreement that around 30% of fistulae failed to mature and that in quoting patency rates this is often underrepresented in the literature.
- There was a discussion about average patency rates for fistulae compared with grafts and comments were made that when taking into account the failure to mature rate, the patency rates for fistulae and grafts are similar at 12 months.
- Catheters are the most expensive access procedure to maintain and suffer from an average rate of infection of 1 per year, each episode of infection costing an average of \$56k. The overall prevalence of haemodialysis presented was thought to be reasonable and the projections of annual growth rate of 4% were felt to be appropriate or even a little conservative.
- It was felt that it is unlikely that the prevalence of graft use will fall below 100,000 patients in the US. The reasons for lower success rates of fistulae in the US compared with Europe were discussed. Important factors were felt to be the population demographics (as already discussed), the higher flow rate used in the US and the competence level of technicians routinely dialysing patients in US centres.
- There was also a discussion on the appropriateness of the KDOQI guidelines going forward. The US vascular surgeons present felt that they had been underrepresented in discussions to date and had not had sufficient influence on the guidelines produced. It was felt that the vascular surgeons should attempt to assert their views more systematically into the process and some commented they felt that the current drive to majority fistula use could potentially harm patients by placing them in inappropriate patients who would then have difficulty with subsequent access in whom the fistulae failed to mature leaving them open to complications from continued catheter access.

"I've got data on 1,700 patients over the last four or five years and it shows that there is no statistical difference between using a fistula and a graft"

3. Trinam Target Product Profile

- It was agreed that if Trinam could deliver a result of doubling patency compared with standard grafts then it would be used in a very large proportion of patients receiving grafts. Critical to this area will be the Pharmaco-economic arguments that can be made.
- Use of Trinam will need to deliver overall cost savings to the Health Care System. It is therefore critical that the phase III development programme adequately covers all the relevant pharmaco-economic issues. This includes examining all the associated costs with graft placement including patient visits, screening, radiology costs, surgeons' professional charges, dialysis and any parallel catheter placement required. A rough estimate of all of these costs was suggested at around \$30-40k per graft placement.
- Ark should examine this area very carefully and ensure that all the relevant data is captured as part of the Phase III programme and a subsequent pharmaco-economic evaluation of Trinam in this setting is produced. The majority of patients in this setting will be treated on an outpatient rather than inpatient basis and this also has implications for subsequent reimbursement of the product following approval. The estimate is that Trinam would be used in 90% of cases in an outpatient setting and in 10% as an inpatient procedure.

4. Customers – how and by whom will Trinam be used

- The various players associated with the potential use of Trinam were discussed and it was agreed that the visual presented by Ark covered all the key players likely to be involved in the decision to use Trinam. Whilst it was felt that nephrologists would have a strong influence on whether Trinam was used and could exert influence by deciding to refer patients to particular surgeons, it was felt unlikely that nephrologists would ultimately determine the type of vascular access to be used. The vascular access surgery itself would be conducted by a number of different types of surgeons. The estimate given was that transplant surgeons would do 30% of the procedures, 30% would be done by vascular surgeons and 40% by general surgeons. It would therefore be important to be able to access all of these surgical customer groups when commercialising Trinam.
- There was a brief discussion held on what type of representative would be most appropriate to see these surgical customers and it was felt that in most cases the representative would need to have experience of selling surgically related products, be able to gain access to the OR and be seen as a competent and credible information partner in the early adoption of Trinam in the surgical setting.
- It was also clear that nephrologists would remain an important group and influence of this group could lead to more rapid and widespread adoption of Trinam. The communication with this customer group would be more of a traditional pharmaceutical 'sell'. It was felt important in the early commercialisation of Trinam to organise training for surgeons and this could be conducted via regional training seminars as well as local training in individual ORs.
- The meeting was closed with thanks to all participants for a very informative and interactive discussion. The next meeting to be held later this year would explore some of the issues raised in greater detail.