ReNeuron
pioneering stem cell therapeutics

Advanced Medical Therapies

The pathway to product approval: new indications

Shaun Stapleton
Head of Regulatory Affairs

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ReNeuron Ltd

- UK based stem cell company
- 65 employees
- Integrated R&D and large-scale GMP manufacturing facility in South Wales

- Enables capacity build for all Phase III needs and initial in-market supply

Llywodraeth Cymru
Welsh Government

New Indications

- Established Indications
  - Established pathway to approval
  - Written guidance on endpoints; safety data; specific guidance on study design
  - Products with Prescribing Information and published Regulatory review data
- New Indications
  - An opportunity for innovative medicines
  - Uncertain development pathway
  - Sponsors have to lead the development of Regulatory guidance and possibly the medical community view on demonstrating safety and efficacy of new products in new indications
    - Takes time and resources - in companies that are often small and with limited time/ funds

ReNeuron examples

- CTX0E03 human neural stem cells
  - Treatment of disability following ischaemic stroke
  - 1-1.5 million strokes per year in EU
  - 40% of survivors have some disability
  - Rehabilitation ineffective after 3-6 months
  - 3.5 million DALYs lost per year in EU (6% of all causes)
  - No available pharmacological (or other) treatment

- Human retinal progenitor cell (hRPC)
  - Treatment of retinitis pigmentosa
  - Rod photoreceptor death and retinal dystrophy
  - Orphan indication (1/4000 prevalence)
  - Average age of onset – 36 years
  - No available treatment

Extent of clinical data needed for approvals - safety

- Safety Database Size
  - New classes of therapies may need greater patient exposure, for a longer period of time, more subgroups of patients
  - Regulatory view may be based on existing classes of products – e.g. haemorrhage relating to thrombolytic medication in stroke
  - Potential new risks – gene therapies; immune modifying products; cell based products
    - Long-term follow up
  - Regulatory view is often linked to size of potential patient group
    - expectations for quantity and duration of safety data for advanced therapies in diabetes, stroke, are similar as for established therapies
    - on the other hand, single dose treatment and local delivery may reduce size of safety database required

Extent of clinical data needed for approvals - efficacy

- Regulatory viewpoint is often based on what they know and what they have been asked to review before
- Advice and expectations on new products and new indications can be inappropriate
  - Sponsor needs to challenge; provide evidence; suggest alternative development pathways with supporting data
  - Challenge of placebo controlled trials
  - Maintenance of effect
- Study size is not necessarily smaller for new indications or advanced therapies
  - Tools/scales and the size of change being looked for can lead to large studies to demonstrate statistical significance
- May not be an existing endpoint/scale that is appropriate
  - Meaningful clinical benefit (MCID) is often not established
  - Trying out new scales in pivotal/registration studies is not recommended!
  - Developing new scales: costly, time consuming – but there are clear Regulatory guidelines on doing this

Sources of data and influence

- Traditional Advisory Boards
  - Regional differences in advice/practice
- Allied medical practitioners can be equally valuable sources of information and guidance
  - in stroke rehabilitation: Physical Therapists and Occupational Therapists
- Patient /carer and expert views on treatment risk and meaningful benefit can be influential and helpful in regulatory discussions
  - Inexpensive to collect this in an organised way
  - Agency meetings
- Collaborate with 'competitor' companies working in the same area to bring interest groups together for discussion and consensus development
  - Industry led
  - Academia / Medical Foundation led

Regulatory Agencies Expedited Programmes

- Early Access to Medicines Scheme in UK
- Conditional MA and adaptive licencing in EU
  - Post-approval gathering of confirmatory safety and efficacy
  - High unmet medical need
  - Benefit of early access outweighs risk
- Conditional MA in Japan
  - Regenerative medicine
  - Safety shown, promise of efficacy
- Accelerated approval and priority review in US
  - Surrogate endpoints
  - Reduced FDA review time

Conclusion

- Innovative medicines in areas of unmet need require innovative approaches
- Regulatory agencies are open to these approaches
  - Sponsors and regulators need to support each other
  - Working with experts, other healthcare staff, patients, and carers
- Expedited programmes can lead to early approvals
- But innovative medicines in new indications doesn't mean lower standards