12 Month Functional Outcome After Intracerebral Implantation of Human Neural Stem Cells (PISCES-2)

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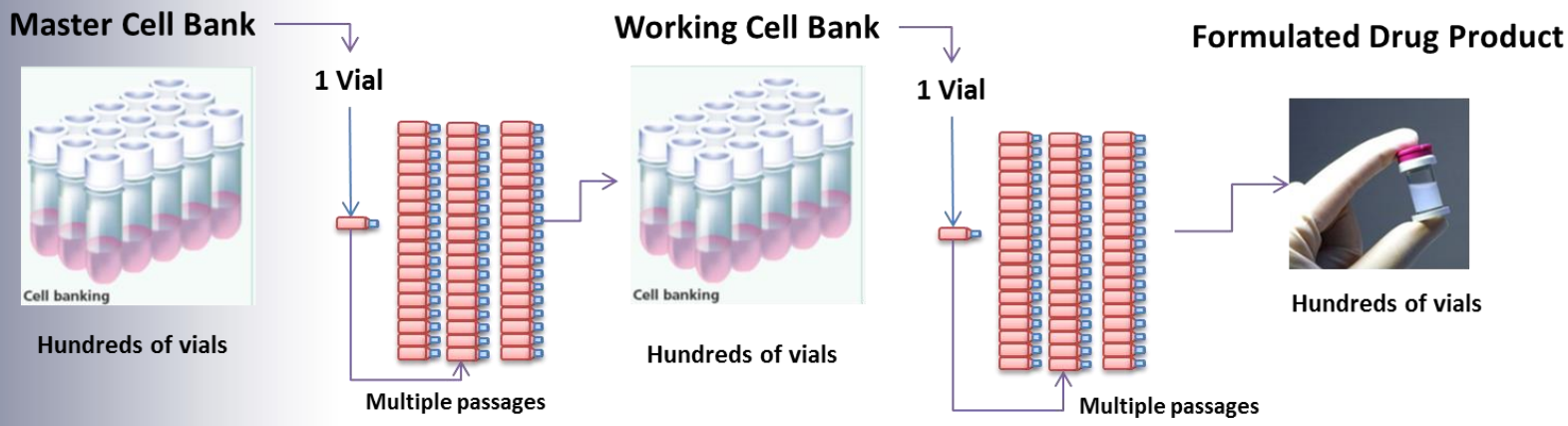
Disclosures

- Chief Investigator for PISCES 1 and 2 trials, ReNeuron Observational Study sponsored by ReNeuron
- Advisory Board for ReNeuron on PISCES 3 design

- Results describe unapproved investigational use of CTX cells

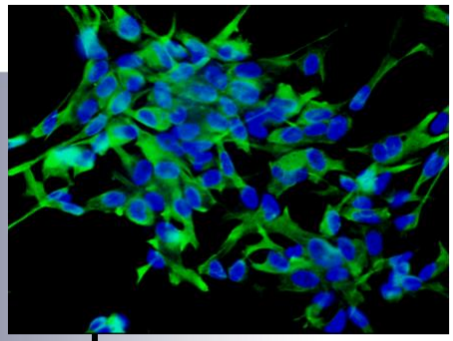
CTX0E03 Cells (CTX0E03 "Drug Product")

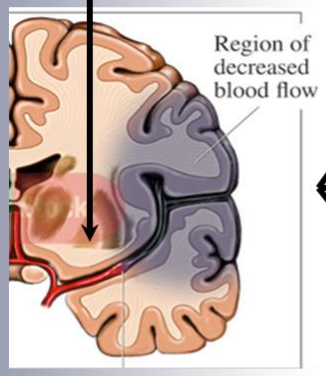
- Allogeneic multipotent human neural stem cell line
- Derived from a single 12 week human foetal cortex tissue sample
- Conditionally immortalised with c-myc under chemical control with 4OH tamoxifen
- Withdrawal of 4OH tamoxifen allows differentiation into all neural cell lineages
- Each patient dose generated by GMP manufacture, frozen and released after testing



CTX0E03 Cells Mechanisms of Action

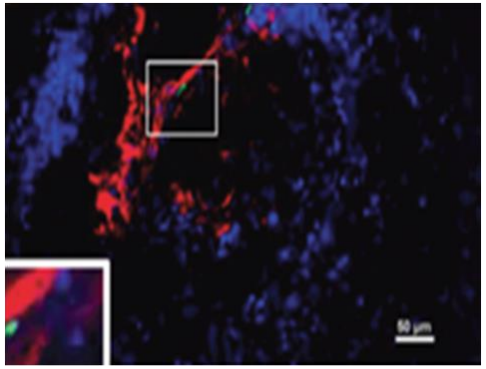
CTX0E03 cells



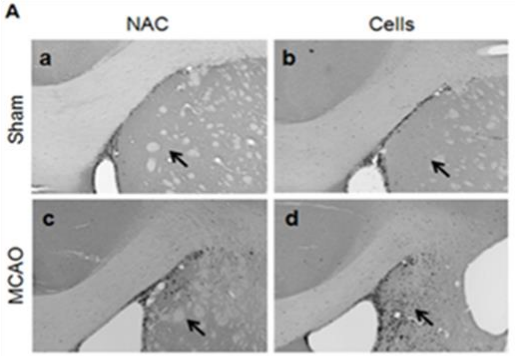


Implanted CTX cells modulate the immune system to promote repair by

Formation of new blood vessels (angiogenesis)



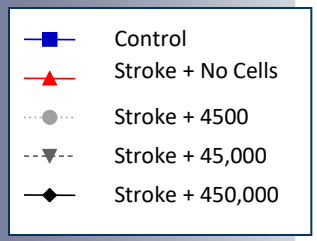
Formation of new neurons (neurogenesis)

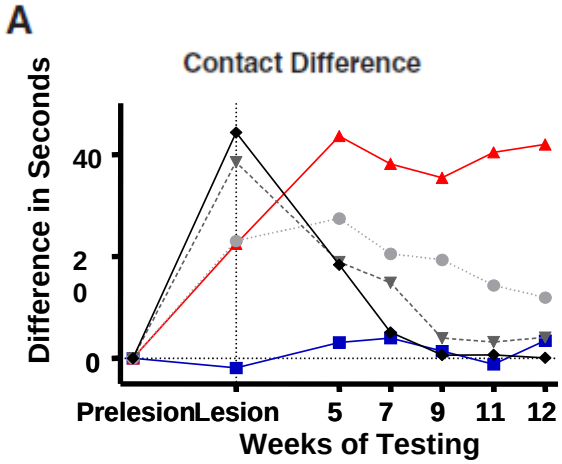


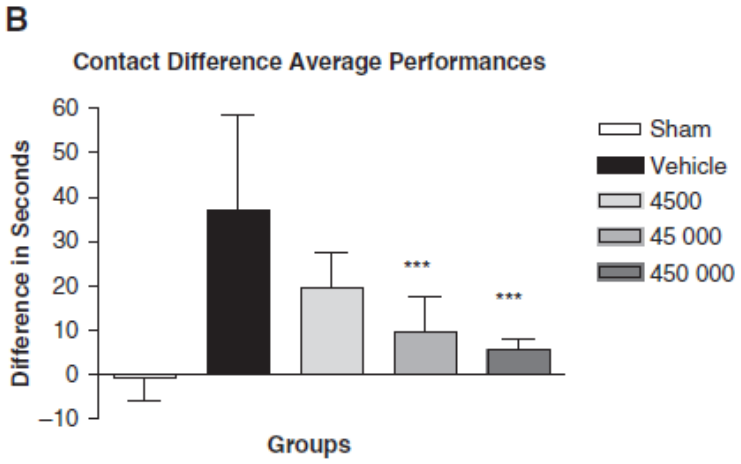
Formation of new connections between neurons (synaptogenesis)

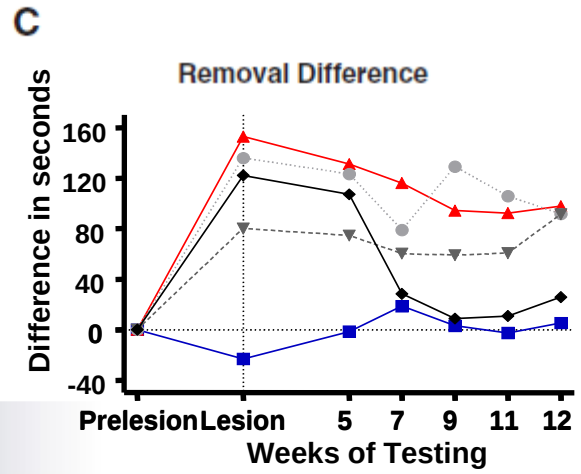
Sinden et al. *Stem Cells Dev*. 2017 26: 933-947.

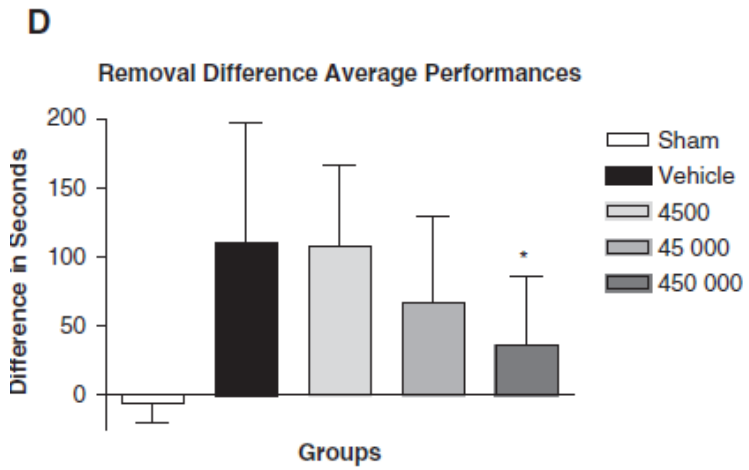
CTX Preclinical Efficacy:
Recovery in Rats After MCA Occlusion Stroke





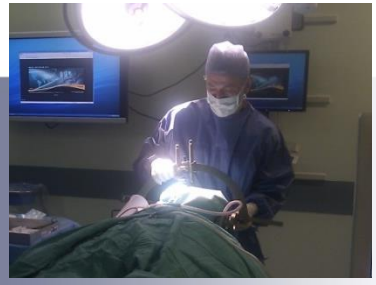


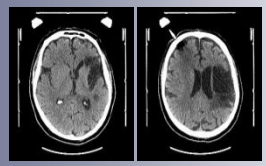


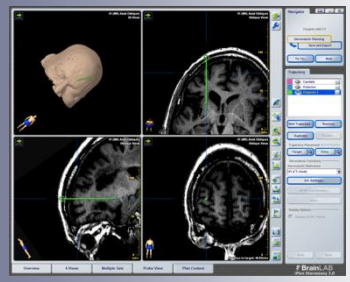


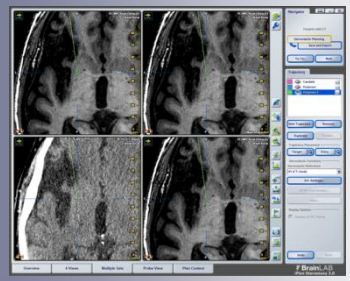
Stroemer et al. *Neurorehabil Neural Repair* 2009 23: 895-909.

PISCES 1 Trial (NCT01151124)









Human neural stem cells in patients with chronic ischaemic stroke (PISCES): a phase 1, first-in-man study

Dheeraj Kalladka, John Sinden, Kenneth Pollock, Caroline Haig, John McLean, Wilma Smith, Alex McConnachie, Celestine Santosh, Philip M Bath, Laurence Dunn, Keith W Muir

www.thelancet.com **Published August 3, 2016** http://dx.doi.org/10.1016/S0140-6736(16)30513-X

- Single centre, open-label, ascending dose Phase 1 study
- Direct stereotaxic implantation of CTX cells into the putamen
- Primary endpoint: Safety (Clinical, Imaging, Immunological)
- Secondary endpoints: Exploratory efficacy (Clinical, imaging)

- Chronic, stable patients median 2.5 years after ischemic stroke involving basal ganglia or subcortical white matter with limb weakness and significant disability

- Single intracerebral doses of CTX-DP induced no cell-related adverse events
- Doses of CTX-DP were associated with improved neurological function
- **Observations supported further investigation of CTX-DP in stroke patients**

Kalladka et al *Lancet* 2016;388:787-96.

PISCES 2 Study Design (NCT02117635)

Aim of the Study:

- To demonstrate effect of CTX cells on improving outcome of patients during rehabilitation phase following an ischaemic stroke
- To provide further safety data in a larger group of patients

Inclusion Criteria

- Male and Female patients ; aged 40-89; 2-12 months after a stroke
- ARAT of 0 or 1
- NIHSS Upper Limb motor score of 4, 3, or 2

Study Procedures

- CTX 20 million cells injected into brain (putamen) on affected side
- Follow up for 12 months
- Physiotherapy minimum 1.5 hours/week for 6 weeks
- Primary Measure: ARAT test #2, 2 point improvement
- Secondary Measures: ARAT, Fugl-Meyer; NIHSS, mRS, Barthel Index

PISCES 2 Endpoints

ARAT Grasp test #2 – placement of a 2.54cm^3 block
3= performs within 5s
2=performs within 5-60s
1=some effort, but does not perform task
0=no part of task completed

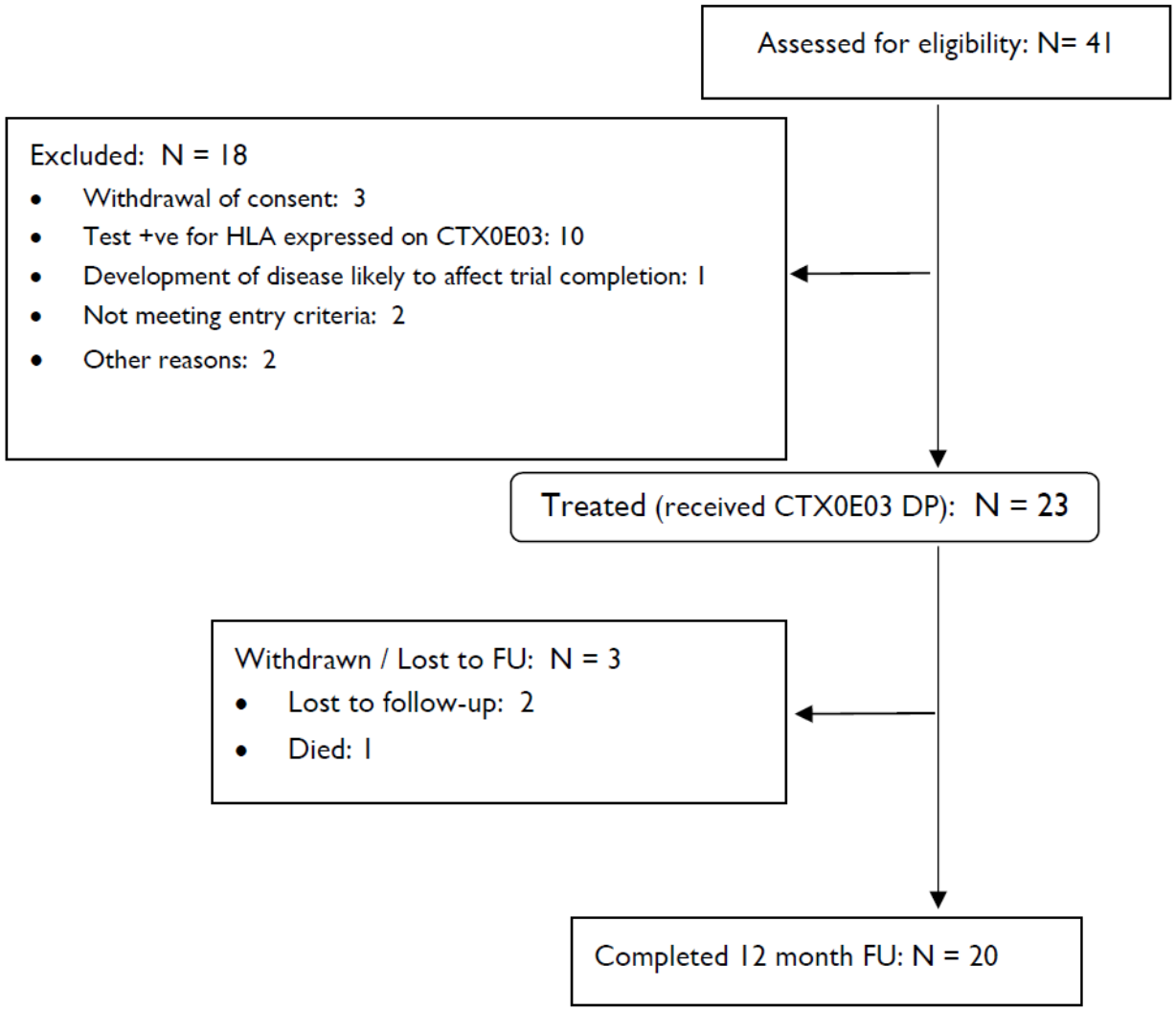
- Primary Measure:
  - ARAT grasp test #2, Responder = 2 point improvement
  - Primary Endpoint: 2 responders at 3 months post-treatment
- Secondary Measures:
  - Total ARAT, Fugl-Meyer; NIHSS, mRS, Barthel-Index

PISCES 2 Study Schedule (by visit)

TREATMENT

	Pre Surgery				Post Surgery						
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
Visit window	Day 28 - (270 ±7) post stroke	Visit 1 + 28d to D300 (+7) post stroke	Up to 7 days prior to surgery	Day 0 within 3m of visit 2	Day 0-2 (First 48h post injection	Day 2	Day 7 (±2)	Day 28 (±4)	Day 90 (±7)	Day 180 (±14)	Day 365 (±30)

PISCES 2 Recruitment and Patient Flow



PISCES 2 Demographics

	N=23
Sex *Male:Female*	13:10
Age *mean±SD, years*	62±11 years (range 41-79)
Affected hemisphere	Left 9; Right 14
Onset to Enrolment *months*	7 (IQR 5, range 2-13)
Medical History	
Hypertension	12 (52%)
Atrial Fibrillation	5 (22%)
Previous Stroke	5 (22%)
Ischemic Heart Disease	3 (13%)
Current or Previous Smoker	16 (70%)
Diabetes	2 (9%)
Peripheral Vascular Disease	2 (9%)

PISCES 2 Stroke Characteristics at Baseline

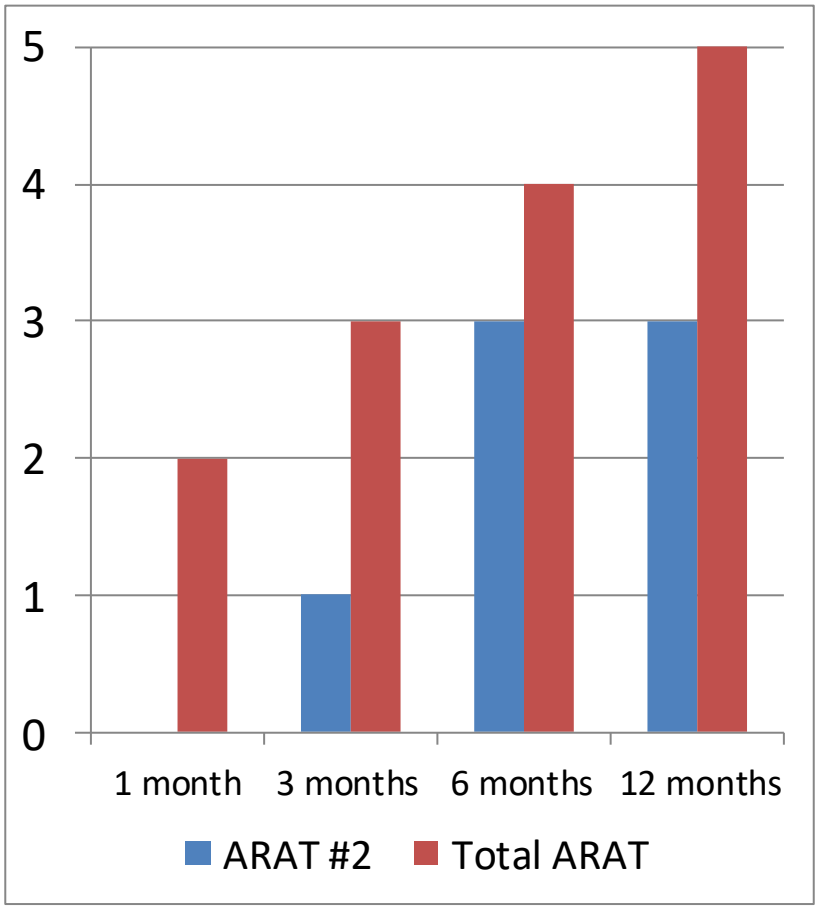
Infarct Location n (%)	
Cortical	12 (52%)
Subcortical	12 (52%)
Basal Ganglia	8 (35%)
Internal Capsule	7 (30%)
Corona Radiata	5 (22%)
Other	2 (9%)
Both cortical and Subcortical	7 (30%)
NIHSS median (range)	**6** (3-15)
UL=2 n (%)	9 (39%)
UL=3 n (%)	5 (22%)
UL=4 n (%)	9 (39%)
Barthel median (range)	**70** (15-100)
mRS median (range)	**3** (2-5)
2 n (%)	3 (13%)
3 n (%)	11 48%)
4 n (%)	8 (35%)
5 n (%)	1 (4%)

PISCES 2 Responder Analysis: Primary and Secondary Measures

Results of Responder analysis	ARAT subtest 2 (grasp) Primary Outcome N=23	ARAT Total Response N=23	Modified Rankin Scale N=23	Barthel Index 100 point scale, Evaluable patients N=17
MCID definition for measures	≥2 point improvement	≥6 point improvement	≥ 1 category improvement	≥ 9 point improvement
1 month	0 (0%)	2 (8.7%)	3 (13.0%)	6 (35.3%)
3 months	1 (4.4%)	3 (13.0%)	7 (30.4%)	8 (47.1%)
6 months	3 (13.6%)	4 (17.4%)	6 (26.1%)	7 (41.2%)
12 months	3 (13.6%)	5 (21.7%)	7 (30.4%)	8 (47.1%)

PISCES 2 Efficacy - ARAT

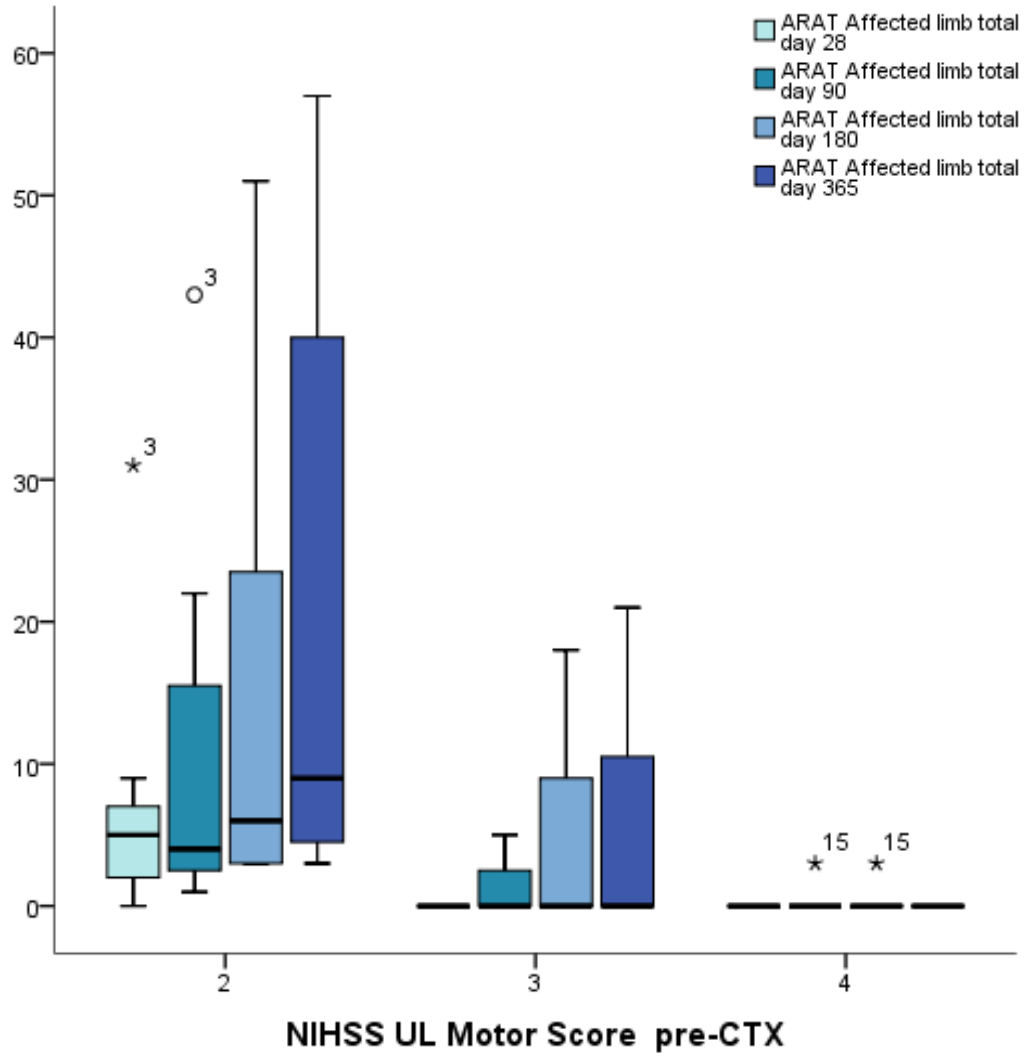
- **ARAT Test #2** ≥ 2 point improvement
  - 3 responders, responding at 3, 6 and 12 months
  - No relapse back to lower score
- **Total ARAT** ≥ 6 point improvement
  - 5 responders, responding at 1, 1, 3, 6 and 12 months



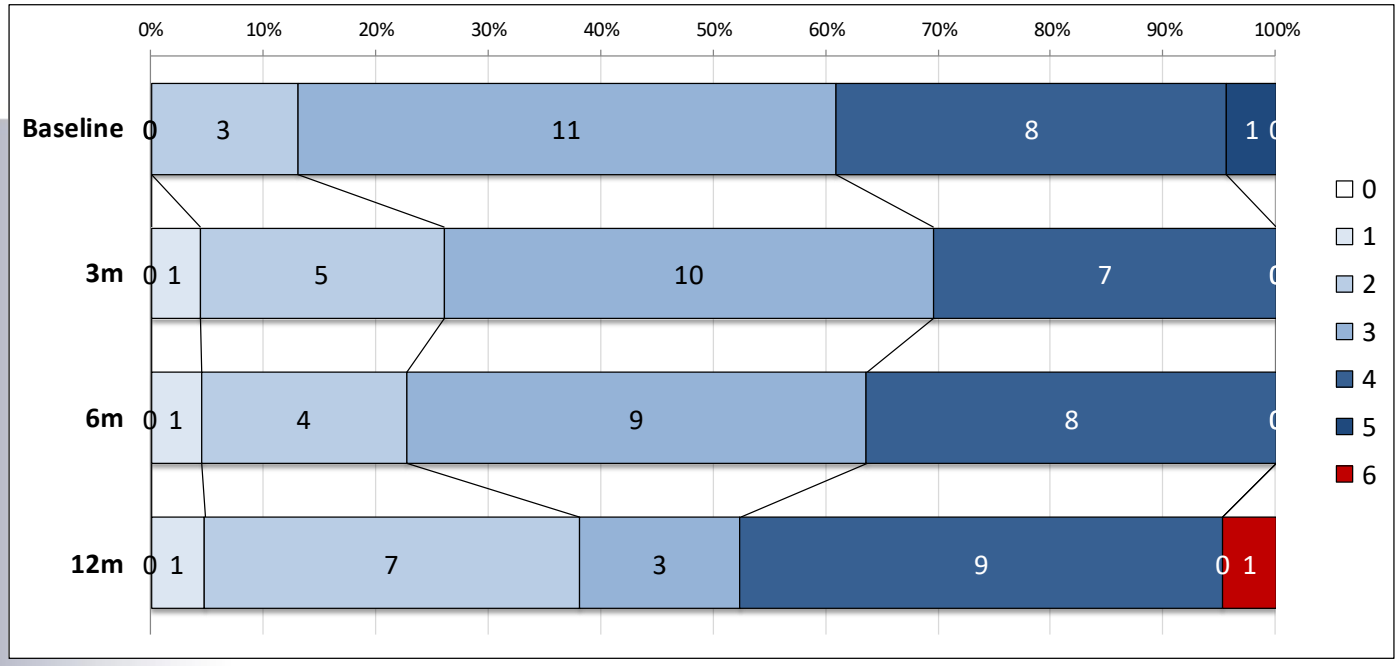
PISCES 2 Efficacy - Median Total ARAT Response by Baseline NIHSS

Total ARAT Affected Limb

- Improvements on ARAT observed in patients with residual movement of the affected arm (NIHSS 2 or 3 at baseline)



PISCES 2 Efficacy – mRS Distribution



NB 12 month mRS outcome determined 1 week prior to suicide in one subject therefore only one death at month 12 shown

- mRS improvement (12m or final measured) compared to baseline in 7 (6 by 1 category, 1 by 2 categories)
- mRS Unchanged in 14, worse (1 category) in 2

PISCES 2 Efficacy – Modified Rankin Scale (mRS) by Baseline NIHSS

- Improvements in mRS greatest in patients with residual movement of the affected arm (NIHSS 2 or 3 at baseline)

Total Subjects			Subjects with NIHSS upper limb score < 4 at baseline (BL)	
Day	N	n* (%)	N	n* (%)
Baseline	23	-	14	-
30	23	3 (13.0%)	14	3 (21.4%)
90	23	7 (30.4%)	14	6 (42.9%)
180	23	6 (26.1%)	14	5 (35.7%)
365	23	7 (30.4%)	14	6 (42.9%)

*number of subjects with at least 1 point improvement in mRS (% of N observed at day of visit)

PISCES 2 Safety: SAEs During Follow-up

System (n subjects)	Event	n Events
Infections (n=5)	Sepsis	2
	Gastroenteritis	1
	LRTI	1
	UTI	1
	Viral	1
CNS (n=5)	Headache	2
	Carotid stenosis	1
	Hypertonia	1
	Ischaemic Stroke	1
	Partial seizure	1
GI (n=1)	Vomiting	1
Procedural (n=1)	Subdural haemorrhage	1
Immunological (n=1)	HLA Positivity	1
Psychiatric (n=1)	Suicide	1
Respiratory (n=1)	Aspiration pneumonia	1

PISCES 2 Conclusions

- Feasibility of subacute treatment with CTX cell implantation at multiple participating sites established
  - Frozen cell product facilitated multicentre trial
- No cell-related safety issues identified
- Trial entry 3-6 months after stroke acceptable to patients
- Functional gains observed in sufficient numbers of participants to justify a randomised, controlled Ph2b trial
  - PISCES 3 to commence 2018

Acknowledgements

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  - University of **Glasgow** (4): KW Muir, L Dunn, W Smith;
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  - University of **Nottingham** (3): N Sprigg, G Dow, G Wilkes;
  - **Newcastle** (2): A Dixit, j Crossman, M Fawcett;
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- **DSMB:** Philip Bath (University of Nottingham), Joanna Wardlaw, Ian Whittle, Chris Weir (all University of Edinburgh)

PISCES 3 Study Design

- IND approved – study to commence in US in HI 2018
- Randomised, placebo-controlled Phase 2b study
- Entry criteria:
  - Ischemic stroke 6-12 months previously
  - modified Rankin Score (mRS) of 3 or 4
  - Some residual Upper Limb movement
- Primary endpoint:
  - Response as measured by mRS six months post treatment
- Key Secondary endpoints
  - Response measured by Barthel Index
  - Improvement in Lower Limb and Trunk function: Timed Up and Go test
  - Improvement in Upper Limb function: Chedoke Arm and Hand Activity Inventory
  - Durability of Response measured out to 12 months