

Late-Breaking Science Oral Abstracts

Thursday, January 25, 2018, 3:30pm – 5:00pm

LATE-BREAKING SCIENCE abstracts/studies presented at the INTERNATIONAL STROKE CONFERENCE 2018:

For late-breaking science being presented at ISC 2018, the embargo lifts when the first presentation begins in the scientific session in which the abstract is being presented: either 11:20 am PST on Wednesday, Jan. 24; 6:30 pm PST on Wednesday, Jan. 24; 11:00 am PST on Thursday, Jan. 25; 3:33 pm PST on Thursday, Jan. 25; or 11:53 am PST on Friday, Jan. 26. News media activities promoting late-breaking science are under embargo until the times noted above.

Presentation Number: LB9

Presentation Title: Alteplase for the Treatment of Acute Ischemic Stroke in Patients with Low NIHSS and Not Clearly-Disabling Deficits: Primary Results of the PRISMS Trial

Author Block: Pooja Khatri, Dawn Kleindorfer, Univ of Cincinnati, Cincinnati, OH; Thomas Devlin, Univ of Tennessee Coll of Med, Chattanooga, TN; Robert Sawyer, Kaleida Health, Buffalo, NY; Matthew Starr, Univ of Pittsburgh Medical Ctr, Pittsburgh, PA; Jennifer Mejilla, Dayton Medical Ctr, Dept of Veterans Affairs, Dayton, OH; Joseph Broderick, Univ of Cincinnati, Cincinnati, OH; Anjan Chatterjee, The Univ of Pennsylvania, Philadelphia, PA; Edward J Jauch, Medical Univ of South Carolina, Charleston, SC; Steven Levine, SUNY Downstate Medical Ctr, Brooklyn, NY; Jose Romano, Univ of Miami Miller Sch of Med, Miami, FL; Jeffrey Saver, UCLA, Los Angeles, CA; Achala Vagal, Univ of Cincinnati, Cincinnati, OH; Barbara Purdon, Jenny Devenport, Genentech, South San Francisco, CA; Andrey Pavlov, Everest Clinical Res, Markham, ON, Canada; Sharon Yeatts, Medical Univ of South Carolina, Charleston, SC

Abstract Body:

BACKGROUND: Over half of acute ischemic stroke (AIS) patients have an NIHSS of 0-5 at presentation. While prior major trials of alteplase included some low NIHSS patients, few with nondisabling deficits were enrolled. We sought to evaluate the safety and efficacy of alteplase in patients with NIHSS 0-5 and deficits judged not “clearly disabling” (defined as inability to return to work or perform basic activities of daily living based on current deficits) in the first randomized trial specific to this population.

METHODS: PRISMS (NCT02072226) was designed as a 948-patient, Phase 3b, double-blind, randomized, placebo-controlled trial of IV alteplase (+ placebo aspirin) compared to placebo alteplase (+ aspirin) at ≤ 3 hours. The primary outcome was 90-day modified Rankin Scale (mRS) 0-1 adjusted for age, treatment time, and NIHSS. The primary safety endpoint was symptomatic intracranial hemorrhage (sICH; any neurological decline attributed to ICH at ≤ 36 hours). The sponsor terminated the study on 21/Dec/2016 (before unblinding) due to delayed recruitment timelines.

RESULTS: From 1/May/2014 to 21/Dec/2016, 313 patients (median age 61 yrs [IQR 52-70], NIHSS 2 [IQR 1-3], and treatment time 2.7 hrs [IQR 2.6-2.7]) were enrolled, including 13% with a final diagnosis of neurovascular mimic. Alteplase-randomized patients were less often male (49 vs 59%) and more often black (22 vs 17%), diabetic (37 vs 28%), and with large artery atherosclerotic etiology (15 vs 7%). Five (3.2%) alteplase-treated patients vs 0 controls had sICH (ARD 3.25% [95% CI 0.75%, 7.38%]). One alteplase-treated patient with concurrent bowel obstruction died (volvulus). At 90 days, 78.2%

alteplase-randomized patients vs 81.5% controls achieved mRS 0-1 (ARD -1.10% [95% CI -9.44%, 7.25%]). In a post hoc calculation, using these data and an uninformative prior, the posterior probability of alteplase benefit is 23%, and that a >6% absolute effect would be observed is 1.9% (95% credible interval of RD -12.2%, 5.5%).

CONCLUSION: Premature termination precludes definitive conclusions. Findings suggest the benefits of alteplase are not likely to extend to patients with low NIHSS without clearly-disabling deficits. There was a significant increase in sICH consistent with alteplase's safety profile.

Author Disclosure Block: **P. Khatri:** Research Grant; Significant; NIH/NINDS. Other Research Support; Significant; Genentech (PRISMS PI effort), Lumosa (DSMB effort, consultation), Biogen (DSMB effort). Expert Witness; Significant; Medicolegal expertise. **D. Kleindorfer:** Speakers' Bureau; Modest; Genentech speaker's bureau. **T. Devlin:** Research Grant; Modest; Neuronal Protection System LLC. Research Grant; Significant; Neuro Analytics, San Bio, Daiichi. Speakers' Bureau; Modest; Corazon. Speakers' Bureau; Significant; Medtronic. **R. Sawyer:** Speakers' Bureau; Modest; Medtronic Speaker's Bureau. **M. Starr:** None. **J. Mejilla:** None. **J. Broderick:** Other Research Support; Modest; monies from Genentech go to my Department of Neurology and Rehabilitation Medicine for my role on PRISMS. **A. Chatterjee:** None. **E.J. Jauch:** Research Grant; Modest; Genentech support for my PRISMS activities. Expert Witness; Modest; Expert testimony in stroke-related cases (modest to negligible). **S. Levine:** Research Grant; Modest; BMS. Research Grant; Significant; NIH, Genentech. Honoraria; Modest; MEDLINK. Expert Witness; Significant; Medical legal cases. Consultant/Advisory Board; Modest; National Stroke Association (no funds), Genentech. **J. Romano:** Research Grant; Modest; Genentech for role as PI of the Mild and Rapidly Improving Stroke Study (MaRISS), NIH for role as PI (MPI) of the MyRIAD study (R01 NS084288), PI (MPI) of the Miami Regional Coordinating Center for StrokeNet (U10 NS086528), PI (MPI) of the Transition of Care Stroke Disparity Stu. Ownership Interest; Modest; Vycor/NovaVision for role as Scientific Advisor. Consultant/Advisory Board; Modest; Genentech for Steering Committee role of the Potential for rtPA to Improve Stroke with Mild Symptoms (PRISMS) Study, Vycor/NovaVision for role as Scientific Advisor. **J. Saver:** Consultant/Advisory Board; Modest; Steering committee. **A. Vagal:** Research Grant; Modest; Co-I NIH/NINDS NS30678. Research Grant; Significant; PRISMS Co-I, Imaging Core Lab, Genentech, Inc. **B. Purdon:** Employment; Significant; Employment at Genentech. **J. Devenport:** Employment; Significant; Employment at Genentech. **A. Pavlov:** None. **S. Yeatts:** Research Grant; Modest; NINDS funding through university to cover statistical effort related to iDEF, DEFUSE 3, and StrokeNet. Other Research Support; Modest; CR Bard Inc funding through university to cover statistical effort related to DSMB participation.

Presentation Number: LB11

Presentation Title: Benefit of Thrombectomy for Stroke with Clinical-Imaging Mismatch at 6-24 Hours in Dawn: Comparison of Patients Selected with Core Infarct Measured by MR-DWI vs CTP-rCBF

Author Block: Cathy A Sila, Univ Hosp Cleveland, Cleveland, OH; David S Liebeskind, Univ of California, Los Angeles, Los Angeles, CA; Ashutosh P Jadhav, Univ of Pittsburgh Medical Ctr, Pittsburgh, PA; Raul G Nogueira, Diogo C Haussen, Emory Univ Sch of Med, Atlanta, GA; Ronald F Budzik, OhioHealth Riverside Methodist Hosp, Columbus, OH; Alain Bonafe, Hop Gui-de-Chauliac, Montpellier, France; Parita Bhuva, Texas Stroke Inst, Dallas-Fort Worth, TX; Dileep R Yavagal, Univ of Miami Miller Sch of Med, Miami, FL; Ricardo A Hanel, Baptist Jacksonville, Jacksonville, FL; Marc Ribo, Hosp Vall d'Hebron, Barcelona, Spain; Christophe Cognard, Univ Hosp of Toulouse, Toulouse, France; Ameer E Hassan, Valley Baptist Medical Ctr, Harlingen, TX; Wade S Smith, Univ of California, San Francisco, San Francisco, CA; Jeffrey L Saver, Univ of California, Los Angeles, Cleveland, OH; Tudor G Jovin, Univ of Pittsburgh Medical Ctr, Pittsburgh, PA

Abstract Body:

Background: The safety and efficacy of revascularization in an extended time window may be more dependent on the size of the core infarct. Some studies suggest that MR-DWI is more accurate than CTP-rCBF for defining core infarct volume but there are no randomized data comparing imaging modalities. **Methods:** Patients within 6-24 hours of last known well (LKW) and an acute occlusion of the intracranial ICA and/or MCA were eligible if they had a clinical-imaging mismatch profile of: age <80 yrs/NIHSS ≥ 20 /core 31-55cc, age <80 yrs/NIHSS ≥ 10 /core <31cc, or age ≥ 80 yrs/NIHSS ≥ 10 /core <21cc. Core infarct volume was assessed with RAPID software and defined as ADC <620 10^{-6} mm²/s or rCBF <30%. Statistics included comparison of baseline characteristics, univariate and multivariate logistic regression analyses. **Results:** The qualifying imaging study for the 206 DAWN patients was MR-DWI in 83 (40.3%) and CTP-rCBF in 123 (59.7%). There was a trend for more patients selected with MR vs CTP to be transferred from another hospital (66.3 vs 53.7%, p=0.084) but otherwise the two imaging groups were well matched for age (70.6 vs 69.6 yrs), NIHSS (17 vs 17), core infarct volume (10 vs 9 cc), time from LKW to randomization (13.4 vs 12.2 hrs), and thrombectomy treatment (55.4 vs 49.6%). There were no significant differences in the safety outcomes of patients selected with MR vs CTP for symptomatic ICH (4.8 vs 4.1%), neurologic deterioration (15.7 vs 22.8%), and fatal stroke (13.3 vs 19.5%) or the efficacy outcome of functional independence at 90 days (mRS 0-2: 34.9 vs 29.3%, weighted mean mRS 4.9 vs 4.2). Multivariate analysis identified thrombectomy treatment, baseline NIHSS, age, and blood glucose as significant predictors of good outcome but there was no significant effect of MR as the imaging modality (OR 1.26 [0.59-2.72], p=0.548) nor an interaction between the imaging modality, time to randomization and outcome (p=0.913). **Conclusions:** The efficacy and safety of thrombectomy for patients in DAWN meeting clinical-imaging mismatch criteria at 6-24 hrs were comparable whether the core infarct was measured by MR-DWI or CTP-rCBF. Future clinical trials aiming to extend eligibility for thrombectomy should include both imaging modalities to determine if these results are generalizable.

Author Disclosure Block: C.A. Sila: Honoraria; Modest; Medtronic. D.S. Liebeskind: Research Grant; Modest; NIH. Consultant/Advisory Board; Modest; Stryker- Imaging Core Lab, Medtronic- Imaging Core Lab. A.P. Jadhav: None. R.G. Nogueira: Other; Modest; Stryker- travel reimbursement. D.C. Haussen: None. R.F. Budzik: None. A. Bonafe: None. P. Bhuva: None. D.R. Yavagal: Consultant/Advisory Board; Modest; Medtronic. R.A. Hanel: Research Grant; Modest; Medtronic. Consultant/Advisory Board;

Modest; Stryker, Medtronic, Microvention. **M. Ribo:** None. **C. Cognard:** Consultant/Advisory Board; Modest; Stryker, Medtronic, Microvention. **A.E. Hassan:** Honoraria; Modest; Medtronic. Consultant/Advisory Board; Modest; Stryker, Medtronic, Penumbra. **W.S. Smith:** Other; Modest; Stryker DSMB Chair. **J.L. Saver:** Consultant/Advisory Board; Modest; Stryker, Medtronic-Abbott, Neuravia. **T.G. Jovin:** Other; Modest; Stryker- travel reimbursement.

Presentation Number: LB12

Presentation Title: Modeled Impact of Bypass to an Endovascular-capable Center on Clinical Outcomes: An Analysis of the STRATIS registry

Author Block: Nils H Mueller-Kronast, Tenet Health Care, Delray Beach, FL; Michael T Froehler, Vanderbilt Univ Medical Ctr, Nashville, TN; Reza Jahan, Univ of California Los Angeles, Los Angeles, CA; Osama O Zaidat, St. Vincent Mercy Hosp, Toledo, OH; David S Liebeskind, Jeffrey L Saver, Univ of California Los Angeles, Los Angeles, CA; STRATIS Investigators

Abstract Body:

Background Timely mechanical thrombectomy (MT) significantly improves clinical outcomes in acute ischemic stroke patients. Patient access to MT can be challenging due to limited endovascular-capable centers (ECCs) available. Patients are usually routed to the closest hospital, requiring transfer to an ECC. Transfers to ECCs have been associated with worse functional outcomes in the STRATIS registry.

Methods STRATIS is a prospective, multicenter registry of patients treated with a stent retriever device within 8 hours of onset. Patients transferred from initial hospital to a STRATIS hospital, had an out-of-hospital stroke, called 911, and had stroke location data were included in this analysis. Workflow times were compared against two modeled bypass scenarios: (i) direct routing to the STRATIS hospital (ii) direct routing to an ECC with the shortest driving time (ideal hospital). For bypass modeling driving times, Google Maps Distance Matrix API was used.

Results A total of 236 patients (mean age 66.4 years; 53.8% male) were included in the preliminary analysis. Median baseline NIHSS was 17; 64.4% received IV-tPA. Among 117 ground transfer patients, the median distance from scene to ECC was 18.6 miles. Direct routing was estimated to increase the median EMS arrival to tPA intervals only by 6 and 2 minutes for STRATIS and ideal hospitals, respectively, while the median interval from EMS to puncture would have decreased by 83 and 88 minutes ($p < 0.001$). The difference for onset to puncture was 87 min less ($p < 0.001$) under ideal bypass, which is predicted to increase good and excellent outcomes from 50.5% to 59.7% and 31.4% to 46.5%, respectively ($p = 0.012$, Rankin shift analysis).

Conclusion Direct bypass to an ECC may significantly shorten treatment times and improve clinical outcomes compared to transfer from a non-ECC, without substantially delaying tPA. This benefit increases for shorter transfers, and even air transfer patients might benefit from bypass

Table. Comparison of time intervals and outcomes, actual transfer by ground vs. modeled bypass to ideal center

Interval/Outcome	Actual transfer by ground Mean ± SD (N) [median] (IQR)	Modeled bypass to ideal center Mean ± SD (N) [median] (IQR)	Actual vs. bypass to ideal center p-value
Distance: scene to initial hospital (mi)	8.1 ± 9.1 (115) [4.0] (2.0,11.0)	-	-
Distance: initial to endovascular hospital (mi)	26.9 ± 25.2 (114) [17.0] (10.3,36.0)	-	-
Distance: scene to endovascular hospital (mi)	-	26.9 ± 26.1 (117) [18.6] (8.5,34.4)	-
EMS scene arrival to initial hospital (min)	25.3 ± 10.9 (81) [23.0] (17.0,32.0)	-	-
EMS scene arrival to endovascular door (min)	170.2 ± 61.8 (109) [165.0] (133.0,194.0)	49.4 ± 26.5 (117) [41.0] (31.0,57.0)	<0.001
EMS scene arrival to IV-tPA (min)	83.0 ± 28.8 (71) [78.0] (67.0,89.5)	86.5 ± 25.3 (73) [80.0] (69.0,93.0)	0.578
EMS scene arrival to arterial puncture (min)	225.1 ± 70.8 (115) [218.0] (183.0,255.0)	138.3 ± 26.6 (115) [130.0] (119.5,145.5)	<0.001
mRS at 90 days (shift analysis)	-	-	0.012
mRS 0-1 at 90 days	31.4% (33/105)	46.5%	-
mRS 0-2 at 90 days	50.5% (53/105)	59.7%	-

EMS scene arrival time interval include imputed measurements for subjects without EMS arrival times measured.

Ideal Center: ≥11 MT procedures billed (all payer) in 2015 and shortest drive time from stroke location.

Author Disclosure Block: **N.H. Mueller-Kronast:** Consultant/Advisory Board; Modest; Medtronic Neurovascular. **M.T. Froehler:** Research Grant; Modest; NIH, Medtronic, Stryker, Microvention. Consultant/Advisory Board; Modest; Medtronic, Stryker, Balt/Blockade Medical, Viz AI, Neurvana. **R. Jahan:** Consultant/Advisory Board; Significant; Medtronic. **O.O. Zaidat:** Consultant/Advisory Board; Modest; Medtronic. **D.S. Liebeskind:** Consultant/Advisory Board; Significant; Medtronic (Imaging Core Lab), Stryker (Imaging Core Lab). **J.L. Saver:** Consultant/Advisory Board; Modest; Medtronic, Stryker, Neuravi.

Presentation Number: LB13

Presentation Title: WEAVE™ Intracranial Stent Trial: Final Trial Results in 150 Consecutive Patients Treated On-Label

Author Block: Michael J Alexander, Cedars-Sinai Medical Ctr, Los Angeles, CA; John C Chaloupka, Mount Sinai Medical Ctr, Miami, FL; Blaise Baxter, Erlanger Medical Ctr, Chattanooga, TN; Alois Zauner, Cottage Medical Ctr, Santa Barbara, CA; Richard Callison, SSM Health System, St. Louis, MO; Shlee Song, Cedars-Sinai Medical Ctr, Los Angeles, CA; Wengui Yu, U.C.I. Medical Ctr, Irvine, CA

Abstract Body:

Introduction: Following the approval trial of the Wingspan® Stent for symptomatic intracranial atherosclerotic disease in which a 4.5% periprocedural complication rate was seen, favorable registry data was reported. Subsequently, a trial using the device in an IDE application, not for its original indication, demonstrated poor clinical results with a 14.7% periprocedural complication rate. The WEAVE (Wingspan Stent System Post Market Surveillance Study) Trial is a prospective trial evaluating periprocedural outcomes in patients with the revised FDA indications for on-label use. This is the largest on-label study of the Wingspan Stent ever conducted in the United States.

Methods: Data for the 197 patients undergoing stenting are included in this report. The primary analysis endpoints included periprocedural stroke or death in patients who were treated on-label. On-label indication included 70% or greater intracranial stenosis, with two prior strokes in the target territory, with one of the events occurring with preventive medical therapy, and stenting greater than 7 days following the most recent qualifying stroke. Patient outcomes were assessed by an independent Stroke Neurologist.

Results: In the 197 consecutive patients enrolled in the trial, 150 patients were treated on-label and are included in the primary analysis, and 47 patients were treated off-label and are included in the secondary analysis. The mean stenosis in the primary analysis group was 83.3%. Of the 150 patients in the primary analysis, 4 patients (2.7%) reached a primary endpoint of stroke, or death within 72 hours. In the off-label group, 11 of the 47 patients (23.4%) reached a stroke or death endpoint within that period. In off-label use, there was a statistically higher rate of complications compared to on-label use, with Fisher exact test, $p < 0.0001$.

Conclusions: The final trial results of the 150 on-label patients of the WEAVE Trial have demonstrated a very low periprocedural morbidity and mortality of 2.7%. This data lends support to the concept that refined patient selection criteria and establishment of best practice techniques and management for these patients can substantially decrease the periprocedural risk of intracranial stenting and benefit these patients clinically.

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Presentation Number: LB14

Presentation Title: Two-year Safety and Clinical Outcomes in Chronic Ischemic Stroke Patients After Implantation of Modified Bone Marrow-derived Mesenchymal Stem Cells (sb623): A Phase 1/2a Study

Author Block: Gary K Steinberg, Stanford Univ, Stanford, CA; Douglas Kondziolka, New York Univ, New York, NY; Lawrence R Wechsler, L D Lunsford, Univ of Pittsburgh, Pittsburgh, PA; Anthony S Kim, Univ of California, San Francisco, San Francisco, CA; Jeremiah N Johnson, Stanford Univ, Stanford, CA; Damien Bates, SanBio, Inc., Mountain View, CA; Gene Poggio, Biostatistical Consulting Inc., Lexington, MA; Casey Case, Michael McGrogan, Ernest W Yankee, SanBio, Inc., Mountain View, CA; Neil E Schwartz, Stanford Univ, Stanford, CA

Abstract Body:

Objective Ischemic stroke is a leading cause of long-term disability. Reports from pilot stage clinical studies indicate that stem cell-based treatments may improve neurological function secondary to chronic stroke.

Methods This was a two-year, open-label, single-arm, Phase 1/2a study (NCT01287936) to evaluate safety and clinical outcomes associated with surgical implantation of modified bone marrow-derived mesenchymal stem cells (SB623) in 18 patients with stable chronic ischemic stroke.

Results All patients experienced at least one treatment-emergent adverse event (TEAE). No patients withdrew due to adverse events, and there were no dose-limiting toxicities or deaths. The most frequent TEAE was headache related to surgical procedure (88.9%). Seven patients experienced nine serious adverse events, which resolved without sequelae. In 16 patients who completed 24 months of treatment, statistically significant improvements from baseline (mean) were reported for: European Stroke Scale (ESS): 5.7 (95% CI, 1.4-10.1; $p < 0.05$), National Institutes of Health Stroke Scale (NIHSS): -2.1 (95% CI, -3.3 to -1.0; $p < 0.01$), Fugl-Meyer (F-M) total score: 19.4 (95% CI, 9.9-29.0; $p < 0.01$), and F-M motor function total score: 10.4 (95% CI, 4.0-16.7; $p < 0.01$) at 24 months. There were no statistically significant changes in the modified Rankin Scale. The size of transient lesions detected by T2 FLAIR imaging in the ipsilateral cortex at Weeks 1-2 post-implantation significantly correlated with improvement of ESS (0.619, $p < 0.05$) and NIHSS (-0.735, $p < 0.01$) at 24 months.

Conclusions In this completed two-year Phase 1/2a study, implantation of SB623 cells in patients with stable chronic stroke was safe and was accompanied by improvements in clinical outcomes.

Key Words Bone marrow-derived mesenchymal stem cells, SB623 cells, stable chronic stroke, stereotactic transplantation, phase 1/2a study

Author Disclosure Block: G.K. Steinberg: Consultant/Advisory Board; Modest; Qool Therapeutics, Peter Lazic US, Inc., NeuroSave. D. Kondziolka: Consultant/Advisory Board; Modest; Elekta AB. L.R.

Wechsler: Research Grant; Modest; Athersys, Inc.. Ownership Interest; Modest; Silk Road Medical, Remedy Pharm. L.D. Lunsford: Ownership Interest; Modest; Elekta AB. Consultant/Advisory Board; Modest; Elekta AB. A.S. Kim: Research Grant; Modest; BioGen Idec. J.N. Johnson: None. D.

Bates: Employment; Significant; SanBio, Inc. G. Poggio: Consultant/Advisory Board; Significant; SanBio, Inc. C. Case: Ownership Interest; Modest; SanBio, Inc. M. McGrogan: Employment; Significant; SanBio, Inc.. Ownership Interest; Modest; SanBio, Inc. E.W. Yankee: Ownership Interest; Modest; SanBio, Inc.. Consultant/Advisory Board; Modest; SanBio, Inc.. N.E. Schwartz: None.

Presentation Number: LB15

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

Author Block: Keith W Muir, Univ of Glasgow, Glasgow, United Kingdom; Diederik Bulters, Univ Hosp Southampton, Southampton, United Kingdom; Mark Wilmot, Queen Elizabeth Hosp Birmingham, Birmingham, United Kingdom; Nikola Sprigg, Univ of Nottingham, Nottingham, United Kingdom; Anand Dixit, Royal Victoria Infirmary, Newcastle, United Kingdom; Nick Ward, Univ Coll London, London, United Kingdom; Pippa Tyrrell, Univ of Manchester, Manchester, United Kingdom; Arshad Majid, Univ of Sheffield, Sheffield, United Kingdom

Abstract Body:

Introduction: Stem cells may promote recovery in chronic stroke. Following a Phase 1 study of cloned human neural stem cells (CTX cells), we undertook a Phase 2 multicenter study (2012-003482-18, PISCES 2) to further investigate the efficacy of cell administration in subacute stroke.

Methods: Patients with supratentorial ischaemic stroke causing upper limb weakness (NIHSS>1) and functional impairment (Action Research Arm Test [ARAT] sub-test number 2 [grasp] 0-1) were recruited 1 to 10 months post-stroke onset. A single dose of 20 million CTX cells was injected by stereotactic surgery into the putamen of the affected hemisphere. Patients were assessed prior to, and at 1, 3, 6, and 12 months post-cell administration. The primary outcome was ≥ 2 point improvement in ARAT sub-test 2, at 3 months. Secondary outcomes included ARAT total score, modified Rankin Scale (mRS), Barthel Index (BI) and safety. Secondary outcomes were numbers of patients that attained a minimal clinically important difference (MCID) for each measure.

Results: 23 patients were treated at 8 hospitals in the UK. Median time between stroke onset and cell administration was 7 months (IQR 6-11.5, range 2-13). Mean age was 65 years (range 41-79), 52% were male, with median NIHSS at enrolment of 7 (IQR 5-8). There was 1 responder in the primary outcome at 3 months and 3 responders at 6 and 12 months. At 12 months, 7 patients improved in the mRS and 8 improved in the BI. No cell-related serious adverse events occurred. Most adverse events were related to surgery.

Conclusions: Meaningful improvements were seen in upper limb function and disability by 12 months after intracerebral cell administration in patients with significant upper limb weakness. These results support the initiation of a randomized controlled study of CTX cells in chronic stroke patients.

Results of Responder analysis	ARAT substest 2 (grasp) Primary Outcome N=23	ARAT Total Response N=23	Modified Rankin Score 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%)

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