Late-Breaking Science Oral Abstracts

Friday, February 19, 2016, 10:30am – 12:00 noon

LATE-BREAKING SCIENCE abstracts/studies presented at the INTERNATIONAL STROKE CONFERENCE 2016:

For late-breaking science being presented at ISC 2016, 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, Feb. 17; 3:30 pm PST on Wednesday, Feb. 17; 6:15 pm PST on Wednesday, Feb. 17; 11:00 am PST on Thursday, Feb. 18; 1:30 pm PST on Thursday, Feb. 18; or 11:53 am PST on Friday, Feb. 19. News media activities promoting late-breaking science are under embargo until the times noted above.

Presentation Number: LB22

Presentation Title: Primary Results of the ACTION Trial of Natalizumab in Acute Ischemic Stroke (AIS)

Author Block: Jacob Elkins, Biogen, Cambridge, MA; Mitchell S Elkind, Columbia Univ, New York, NY; Roland Veltkamp, Imperial Coll London, London, United Kingdom; Joan Montaner, Vall d'Hebron Res Inst, Barcelona, Spain; S C Johnston, Univ of Texas, Austin, TX; Aneesh B Singhal, Massachusetts General Hosp, Boston, MA; Kyra Becker, Univ of Washington, Seattle, WA; Maarten G Lansberg, Stanford Univ Medical Ctr, Stanford, CA; Ih Chang, Weihua Tang, Sarah Gheuens, Lahar Mehta, Biogen, Cambridge, MA

Abstract Body: INTRODUCTION: Brain ischemia triggers an inflammatory reaction that worsens outcomes in experimental stroke models.

HYPOTHESIS: Natalizumab, an antibody that reduces acute brain inflammation in multiple sclerosis, will reduce infarct volume and improve clinical outcomes after AIS.

METHODS: ACTION was a 90-day, proof-of-concept, multicenter, double-blind, parallel-group phase 2 study evaluating the efficacy and safety of a single dose of natalizumab in AIS patients. Subjects were randomized 1:1 to receive 300 mg IV natalizumab (n=79) or placebo (n=82) within 9 hours from when they were last known normal. The primary endpoint was relative change in infarct growth from baseline to day 5 assessed by MRI. Secondary and exploratory clinical endpoints were also assessed.

RESULTS: Overall, median baseline National Institutes of Health Stroke Scale (NIHSS) score was 12 and median time to natalizumab treatment was 6 hours. Median baseline infarct volume was 23.68 mL (natalizumab) and 23.41 mL (placebo). Natalizumab did not affect infarct volume growth compared with placebo (relative growth ratio: day 5, 1.09 [P=0.779]; day 30, 1.06 [P=0.684]). However, on secondary outcomes, more subjects on natalizumab than on placebo had an excellent outcome on the modified Rankin Scale (score ≤1 out of 0-6) at days 30 (odds ratio [OR] 2.88; 90% [prespecified] confidence interval [CI] 1.20-6.93) and 90 (OR 1.48; 90% CI 0.74-2.98). More subjects on natalizumab-than on placebo also had an excellent outcome on the Barthel Index (score ≥95 out of 100) at day 90 (OR 1.91; 90% CI 1.07-3.41). Similar benefits favoring natalizumab were seen on the Stroke Impact Scale-16 and the Montreal Cognitive Assessment, although no between-group differences in NIHSS score were observed. The incidences of death (natalizumab 18% [n=14]; placebo 16% [n=13]) and serious adverse events (natalizumab 46% [n=36]; placebo 46% [n=38]) were similar.

CONCLUSIONS: While a single dose of natalizumab administered up to 9 hours after stroke onset did not reduce focal infarct volume growth, treatment was associated with improvements in clinical outcomes over 90 days. These results support further natalizumab studies in AIS.

Author Disclosure Block: **J. Elkins:** Employment; Significant; Current Employee of Biogen. **M.S.V. Elkind:** Consultant/Advisory Board; Modest; Biogen, Biotelemetry/Cardionet, BMS-Pfizer Partnership, Boehringer-Ingelheim,

Sanofi-Regeneron Partnership. Other; Modest; Associate Editor for Neurology, Royalties from UpToDate. **R. Veltkamp:** Other Research Support; Modest; Bayer, BMS, Boehringer Ingelheim, Daiichi Sankyo. Honoraria; Modest; Boehringer Ingelheim, Biogen, BMS, Pfizer, Daiichi Sankyo, Medtronic. Ownership Interest; Significant; Bayer Stock Holder. Consultant/Advisory Board; Modest; Boehringer Ingelheim, Biogen, Pfizer, Medtronic, Morphosys. **J. Montaner:** Other; Modest; Spanish Coordinator ACTION Trial for Biogen. **S.C. Johnston:** Other Research Support; Modest; Astrazeneca. **A.B. Singhal:** Other Research Support; Modest; Boehringer Ingelheim. Honoraria; Modest; Sun Pharmaceuticals, Medlink, UptoDate. Ownership Interest; Significant; Stock options Biogen. Consultant/Advisory Board; Modest; Biogen, Doch Technologies. **K. Becker:** Consultant/Advisory Board; Modest; Merck, Biogen. **M.G. Lansberg:** Honoraria; Modest; Biogen. **I. Chang:** Employment; Significant; Biogen. Ownership Interest; Modest; Biogen Stock Options. **W. Tang:** Employment; Significant; Biogen. Ownership Interest; Modest; Stock Options Biogen. **S. Gheuens:** Employment; Significant; Biogen. Ownership Interest; Modest; Stock Options Biogen. **L. Mehta:** Employment; Significant; Biogen. Ownership Interest; Modest; Stock Options Biogen.

LATE-BREAKING SCIENCE abstracts/studies presented at the INTERNATIONAL STROKE CONFERENCE 2016:

For late-breaking science being presented at ISC 2016, 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, Feb. 17; 3:30 pm PST on Wednesday, Feb. 17; 6:15 pm PST on Wednesday, Feb. 17; 11:00 am PST on Thursday, Feb. 18; 1:30 pm PST on Thursday, Feb. 18; or 11:53 am PST on Friday, Feb. 19. News media activities promoting late-breaking science are under embargo until the times noted above.

Presentation Number: LB23

Presentation Title: IV Alteplase in MR-selected Patients With Stroke of Unknown Onset is Safe and Feasible: Results of the Multicenter MR WITNESS Trial (NCT01282242)

Author Block: Lee H Schwamm, Ona Wu, Massachusetts General Hosp, Boston, MA; Shlee Song, Cedar Sinai Hosp, Los Angeles, CA; Lawrence Latour, NINDS Intramural Stroke Program, Bethesda, MD; Andria Ford, Washington Univ at St Louis, St Louis, MO; Amie Hsia, NINDS Intramural Stroke Program, Bethesda, MD; Alona Muzikansky, Rebecca Betensky, Michael Lev, Pedro Pinto, Gregoire Boulouis, Gordon Harris, Massachusetts General Hosp, Boston, MA; Steven Warach, Dell Medical Sch, Uuniversity of Texas, Austin, Austin, TX; for the MR WITNESS Investigators

Abstract Body: Intro: Many patients with unwitnessed stroke onset are IV tPA ineligible because of timing alone. DWI Positive, FLAIR negative (DPFN) infarction is predictive of stroke duration < 4.5 hr. We sought to determine the safety of IV tPA in patients with DPFN infarct on MR treated within 4.5 hr of symptom discovery.

Methods: Subjects were recruited from 10 sites between Jan 2011-Oct 2015. Subjects were enrolled who qualified clinically per AHA guidelines for IV tPA in the 3-4.5 hr window, were >4.5 hr but <24 hr since last seen well, had a DPFN pattern and could get tPA 0.9 mg/kg <4.5 hr since symptom discovery. FLAIR negative cases had no ischemic signal on FLAIR or subtle signal with a ratio <1.15 of a lesion ROI divided by a mirror-image ROI in the opposite hemisphere. Primary outcome was a rate of symptomatic ICH (sICH) below the upper 95%CI of sICH seen in ECASS3, defined as any intracranial hemorrhage with 4 point increase in NIHSS or causing death; secondary outcome was rate of symptomatic brain edema. Good outcome was pre-specified as mRS 0-1 at 90 d. Univariate comparisons were by Fisher's exact for categorical and Wilcoxon for continuous variables.

Results: Among 80 subjects who received full dose tPA at a median 11.5 hr since last seen well, safety outcomes were comparable to ECASS3, with 1 case of sICH [1.25% (95%CI 0.03%-6.80%) vs. ECASS3 5.30% (95%CI 3.30%-7.80%; p=0.15)] and 1 of symptomatic edema. Median mRS was 2.0 at 90 d and Barthel 95. Asymptomatic ICH (aICH) on 24 hr CT scan occurred in 19/80 (23.8%) subjects (HI1 7, HI2 6, PH1 2, PH2 2, SAH 2). Compared to those without aICH, those with any aICH <90 d had more cardioembolic and large artery strokes, AF, higher median INR, SIR and NIHSS, and worse mRS scores.

Conclusion: IV tPA 0.9 mg/kg given beyond 4.5 hr since last seen well is safe and feasible in patients with unwitnessed stroke selected by MR imaging who can be treated <4.5 hr from symptom discovery. Further research is needed to determine if this cohort derives clinical benefit from treatment.

Table. Patient characteristics and clinical outcomes among tPA treated patients with unwitnessed stroke onset and DPFN pattern, comparing those without ICH vs. any ICH ≤90 d. The characteristics of the tPA treated group from ECASS3 are provided for context.

	All MR WITNESS Patients (n=80)	Patients without any ICH (n=51)	Patients with any ICH ≤90 d (n=29)	p-value	ECASS3 tPA treated cases (n=418)
Age, mean yr (S.D.)	67.5 (13.5)	68.6 (12.3)	65.4 (15.3)	0.49	64.9 (12.2)
Male Gender (%)	56.3	58.2	51.7	0.66	63.2
Medical History (%)					
-Atrial Fibrillation	27.5	15.7	48.3	0.003	12.7
-Diabetes Mellitus	28.75	29.4	27.6	1.00	14.8
-Hypertension	75.0	70.6	82.8	0.29	62.4
-Previous stroke	15.0	17.7	10.3	0.52	7.7
-Current Smoker	22.5	27.5	13.8	0.26	30.6
Stroke Subtype (%)				0.002	
-Large artery atherosclerosis	15	9.8	24.1		
-Cardioembolic	33.8	25.5	48.2		
-Small artery occlusion	25	39.2	0		
-Stroke of other determined etiology	2.5	12.0	3.5		
-Stroke of undetermined etiology	18.8	15.7	24.1		
NIHSS, median (IQR)	7.50	6.00	16.00	<0.001	9.00
Initial Labs, median					
-International normalized ratio	1.00	1.00	1.09	0.004	
-Glucose	120.0	114.0	130.0	0.18	
-Systolic Blood Pressure	156.0	161.0	149.0	0.11	152.6
-Diastolic Blood Pressure	83.0	83.0	84.0	0.97	84.4
tPA Treatment					
-Time since last seen well, median hr	11.45	11.75	11.23	0.39	4.0
-Time since Sx discovery, median hr	3.50	3.18	3.55	0.10	
Imaging Findings					
-Site recorded FLAIR SIR	1.08	1.07	1.10	0.01	
-Symptomatic ICH (%)	1.25 (0.03-6.80)	0	3.5	0.36	5.3 (3.30-7.80)
-Any ICH at 24 hr CT scan (%)	25.0	0	69.0	0.0001	27.0
-HI1 or HI2			13		
-PH1, PH2 or SAH			6		
-Symptomatic edema (%)	1.25 (0.03-6.80)	4.76	0.00	0.36	6.9 (4.70-9.81)
Clinical Outcomes (n=72)					
mRS Score at discharge, median	4.00	3.00	4.00	<0.0001	
mRS Score at 30d, median	3.00	2.00	4.00	<0.0001	
mRS Score at 90d, median	2.00	2.00	3.00	0.005	
mRS (0-1) at 90 d, (%)	34.7	41.8	24.1	0.14	52.4
Barthel Index at 90 d, median	95.00	100.00	85.00	0.04	
Mortality (%)	9.7	1.4	8.3	0.02	7.7

Preliminary results only; final data will be available by ISC. ICH, intracranial hemorrhage; HI, hemorrhagic infarction, PH, parenchymal hematoma; SAH, subarachnoid hemorrhage; mRS, modified Rankin Scale; Sx, symptom

Author Disclosure Block: L.H. Schwamm: Research Grant; Significant; PI of MR WITNESS trial supported by NINDS P50 NS051343 with alteplase provided free of charge plus supplemental site payments by Genentech. Consultant/Advisory Board; Significant; DSMB Penumbra Separator 3D trial, Intl Steering Committee DIAS 3&4, Lundbeck. **O. Wu:** Research Grant; Significant; NIH P50NS051343, R01NS059775, R01NS082285,. Other Research Support; Significant; Gnenetech provides additional site supplemental payments for MR WITNESS and support for a parallel expanded selection arm of the trial. **S. Song:** Research Grant; Modest; Genentech- PRISMS Site PI, MRWITNESS Site PI, California Community Foundation Grant, POSITIVE Site PI. **L. Latour:** None. **A. Ford:** None. **A. Hsia:** None. **A. Muzikansky:** Research Grant; Significant; NINDS P50 NS051343. **R. Betensky:** Research Grant; Significant; NINDS P50 NS051343. **M. Lev:** Research Grant; Significant; NINDS P50 NS051343. **P. Pinto:** None. **G. Boulouis:** None. **G. Harris:** Research Grant; Significant; NINDS P50 NS051343. **S. Warach:** None.

LATE-BREAKING SCIENCE abstracts/studies presented at the INTERNATIONAL STROKE CONFERENCE 2016:

For late-breaking science being presented at ISC 2016, 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, Feb. 17; 3:30 pm PST on Wednesday, Feb. 17; 6:15 pm PST on Wednesday, Feb. 17; 11:00 am PST on Thursday, Feb. 18; 1:30 pm PST on Thursday, Feb. 18; or 11:53 am PST on Friday, Feb. 19. News media activities promoting late-breaking science are under embargo until the times noted above.

Presentation Number: LB24

Presentation Title: GAMES (Glyburide Advantage in Malignant Edema and Stroke) RP Trial: Intermediate Endpoint Analysis as Proof-of-Concept

Author Block: W. Taylor Kimberly, Massachusetts General Hosp, Boston, MA; Jordan J. Elm, Medical Univ of South Carolina, Charleston, SC; Ruediger von Kummer, Univsklinikum Carl Gustav Carus, Dresden, Germany; Andrew Demchuk, Univ of Calgary, Calgary, AB, Canada; Javier Romero, Massachusetts General Hosp, Boston, MA; Holly Hinson, Oregon Health & Science Univ, Portland, OR; Bradley Molyneaux, Univ of Pittsburgh Medical Ctr, Pittsburgh, PA; Lauren Beslow, Gordon Sze, Yale Univ, New Haven, CT; Ann-Christin Ostwaldt, Massachusetts General Hosp, Boston, MA; Gregory del Zoppo, Univ of Washington, Seattle, WA; J. Marc Simard, Univ of Maryland, Baltimore, MD; Kevin Sheth, Yale Univ, New Haven, CT; GAMES Investigators

Abstract Body: Background: Patients with large territory ischemic stroke are at high risk for cerebral edema and death but there is no available pharmacotherapy for its prevention. In the GAMES-RP trial, we evaluated pre-specified intermediate endpoints to assess the mechanism of action for intravenous glyburide (RP-1127).

Objective: The primary objective of this pre-specified analysis was to evaluate the effect of glyburide treatment on imaging and plasma endpoints.

Design: The GAMES-RP trial was a prospective, double blind, randomized, placebo controlled phase 2 study.

Population studied: Patients age 18 to 80 years who presented to 18 U.S. centers with baseline stroke lesion volumes between 82 and 300 cm3 on magnetic resonance imaging were randomized 1:1 to study drug or placebo. The target time from symptom onset to drug infusion was ≤ 10 hours.

Intervention: Patients were treated with either RP-1127 (n=44) or placebo control (n=39) as a bolus followed by a continuous 72 hour infusion, administered within a target of 10 hours.

Outcome measure: The outcome measures were midline shift, total matrix metalloproteinase-9 (MMP-9) levels during the study drug infusion and adjudicated hemorrhagic transformation (HT) designations.

Results: Subjects treated with intravenous glyburide had decreased midline shift at 72-96 hours (4.4 ± 3.6 mm versus 8.8 ± 4.9 mm, p=0.0006). MMP-9 was lower in the RP-1127 treatment arm compared to placebo (211 ng/mL versus 345 ng/mL, p=0.006). Additional analyses related to HT and MMP-9 will be presented.

Conclusions and Relevance: Our data provide proof-of-concept information about the mechanism of action of intravenous glyburide and informs future clinical trial design.

Registry: NCT01794182

Author Disclosure Block: **W. Kimberly:** Research Grant; Significant; Remedy Pharmaceuticals, NIH / NINDS, American Heart Association. **J.J. Elm:** None. **R. von Kummer:** None. **A. Demchuk:** None. **J. Romero:** None. **H. Hinson:** Research Grant; Modest; Remedy Pharmaceuticals. **B. Molyneaux:** Research Grant; Modest; Remedy Pharmaceuticals. **L. Beslow:** None. **G. Sze:** None. **A. Ostwaldt:** None. **G. del Zoppo:** None. **J. Simard:** Ownership Interest; Significant; Remedy Pharmaceuticals. Consultant/Advisory Board; Significant; Remedy Pharmaceuticals. **K. Sheth:** Research Grant; Significant; Remedy Pharmaceuticals.