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DAWN™ Trial Update – SVIN October 26, 2013

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Stroke: *Our Only Focus.Our Ongoing Promise.*

Disclosures

- Silk Road Medical - Consultant
- Stryker NV - DAWN™ Trial Co-PI

Why DAWN™ Trial? Why Now?

To *Expand the indication* of TREVO 2 embolectomy device beyond 8 hrs in appropriately selected patients

To *Prove clinical efficacy* of mechanical embolectomy based on physiological data in a patient population with presumed poor natural history in whom there are currently no treatment options

To *Change guidelines* evidence is needed from one (or more) positive RCTs

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DAWN™ Trial Overview

Complete Stroke Care™

Study Design Overview

DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention

Objective: To demonstrate superior *clinical outcomes* at 90 days with Trevo plus medical management compared to medical management alone in *appropriately selected* patients *treated 6-24 ho*urs after last seen well

Design: Prospective, randomized (1:1), multi-center, Phase II/III (feasibility/pivotal), adaptive, population enrichment, blinded endpoint, controlled trial

Sites: 50 sites (US & EU) maximum

Patients: 150 (feasibility) up to 500 (pivotal) max

Endpoint: Difference in *average weighted* mRS at 90 days between treatment & control in the *enriched* patient population

Unique Design Elements

Clinical Imaging Mismatch - standardizes clinical imaging to select patients

Bayesian Adaptive Design - uses data as it is collected to adjust predicted probability of success/failure at frequent interim analyses (Q 50 pts)

Combined Feasibility/Pivotal - increased efficiency; recalibrate decision to continue to pivotal phase based on real data/signal strength

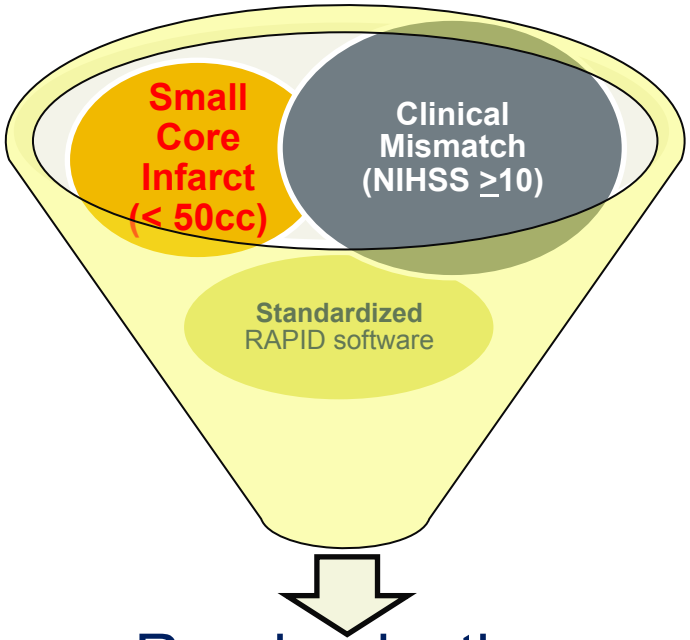
Weighted mRS Endpoint - captures health state transitions across the entire spectrum (more sensitive measurement)

mRS	0	1	2	3	4	5	6
Weight	**10**	**9.1**	**7.6**	**6.5**	**3.3**	**0**	**0**

Enrichment – allows us to fine tune the patient population

Potential Sub groups (based on infarct size):
0-50 cc → 0-45 cc → 0-40 cc → 0-35 cc → 0-30 cc

Clinical Imaging Mismatch



Randomization
Balanced re: Infarct size, time, and ICA vs M1

Why Clinical Mismatch?

- Literature supports core infarct size being predictive of outcomes
- No gold standard to define salvageable brain tissue
- NIHSS assessment (clinical deficit) represents tissue at risk in real time, can be easily administered (and repeated) multiple times, and is validated in clinical practice

Why RAPID?

- In clinical practice, the multi-modal imaging maps (settings/ thresholds) are used to “explore” underlying patho-physiology and determine a treatment plan for an individual patient.
- In an RCT it is essential to standardize these settings/thresholds across all sites/patients, to eliminate selection bias & ensure measured outcomes are a result of the “treatment” being tested.
    - Physician still needs to review result, and decide whether software is returning a legitimate/realistic value and make the final decision about enrolling a patient in a trial.

Why Adaptive Design?

- Unknown Natural History = Unknown treatment effect
- Interim analyses allow us to “fine tune” or “enrich” the patient population (to eliminate patients not being helped/being harmed by treatment)
- Novel weighted mRS endpoint

Clinical Evidence

CONTROL Arm Estimates*			Treatment Arm Estimates		
Study	ICA/M1	mRS 0-2	Study	ICA/M1 +	mRS 0-2
Germans Trias Barcelona	6-24 hr	17.4%	SWIFT	0-8 hr (all comers)	37%
STOP Stroke**	0-8 hr	18.4%	TREVO 2	0-8 hr (all comers)	39.9%
FIRST	0-8 hr	20.4%	Pre-DAWN	8-24 hr	40%
PROACT II	0-6 hr (+ M2)	25%			

*Late presenting patients presumed to have good collaterals and better outcomes **Studies using imaging selection

Expected Treatment Effect = 10-15%

Preliminary Data for the DAWN™ Trial

Imaging Based Endovacular Therapy for Proximal Anterior Circulation Occlusions >8 Hours from LSW in 237 Stroke Patients

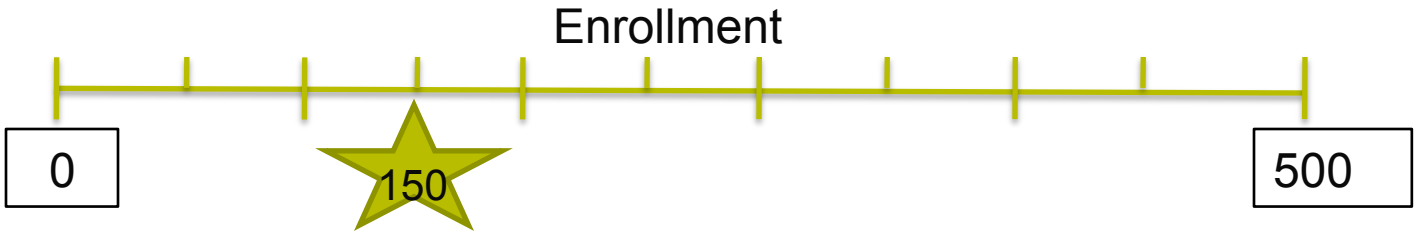
A total of 169 patients from the original cohort met the following criteria:

- Baseline NIHSS score ≥10
- ICA or MCA-M1 occlusion +/-cervical occlusion
- TLSWT between 8-24 hours
- MRI or CTP Selection (vs. CT in PROACT-II)

Jovin TG, Nogueira RG et al., *Stroke*, 2011

Age (years) Mean±SD Median Range	 64±16 68 19-91
Baseline NIHSS Score Mean±SD Median	 17±4 17
Gender % (n) Male Female	 46% (78) 54% (91)
TLSWT Mean±SD Median (IQR)	 12.6±3.7 12 (9.5-14.4)
Site of Occlusion (%) MCA-M1 ICA-T Tandem ICA/MCA Tandem ICA/ICA-T	 54% (91/169) 22% (38/169) 17% (26/169) 7% (12/169)
TIMI 2-3 Revascularization	74% (125/169)
Symptomatic ICH	10% (17)
90-day mRS ≤2	40% (57/142)
90-day mRS ≤3	58% (82/142)
90-day Mortality	25% (42/167)

Sample Size Estimates



Effect size	1.25	1	0.75	0.5	0
Expected Sample size	302	358	401	408	331

Expected Range

Possible Range

Failure

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DAWN Trial ™ Status

Complete Stroke Care ™

Status

- Over 100 sites received questionnaire
- Site qualifications in process
- Site selection is based on multiple criteria
  - Case volume
  - Experience
  - Geography
  - Institutional variety
  - Research resources
  - Speed to start up
- Target for first enrollment: February 2014

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Thank you

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