A New Day DAWNs: Innovative Approaches to NeuroClinical Trial Design

Jeffrey L. Saver, MD, SA Vice-Chair and Professor of Neurology, DGSOM at UCLA

Roger J. Lewis, MD Vice-Chair and Professor of Emergency Medicine, DGSOM at UCLA

NINDS Clinical Trial Methodology Course Keynote
Disclosures

• **JLS**
  » Employee of the University of California. The University of California has patent rights in retrieval devices for stroke.
  » Unpaid site investigator in multicenter trials run by Medtronic, Stryker, and Neuravia, for which the UC Regents received payments on the basis of clinical trial contracts for the number of subjects enrolled.
  » Receives funding for services as a scientific consultant regarding trial design and conduct to Medtronic/Covidien, Stryker, Neuravi, BrainsGate, Pfizer, Squibb, Boehringer Ingelheim (prevention only)
  » Serves as an unpaid consultant to Genentech advising on the design and conduct of the PRISMS trial; neither the University of California nor Dr. Saver received any payments for this voluntary service.

• **RJL**
Talk Outline

- Two Major Challenges in the Design of Pivotal Neuroclinical Trials (JLS)
  - Mapping the Responder Population
  - Outcome Measure Selection
  - Planning of DAWN as an example

- New Approaches to these Challenges (RJL)
  - Mapping the Responder Population
  - Outcome Measure Selection
  - Planning of DAWN as an example

- A New Day DAWNs (JLS)
Two Major Challenges in the Design of Pivotal Neuroclinical Trials

Jeffrey L. Saver, MD,
SA Vice-Chair and Professor of Neurology, DGSOM at UCLA

NINDS Clinical Trial Methodology Course Keynote
The Neurotherapeutic Age

- Neurology now an emphatically and powerfully therapeutic discipline
  - 1988 – “Diagnose and adios”
  - 2017 – “Greet and treat”
  - Due to RCTs
- Therapies available for
  - 7 of the 8 leading neurologic diseases
  - 91% of the worldwide neurologic burden of disease

<table>
<thead>
<tr>
<th>Global Neurologic Burden of Disease (DALYs) - Top 8 Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Migraine/Headaches</td>
</tr>
<tr>
<td>Epilepsy</td>
</tr>
<tr>
<td>Alzheimer and other Dementias</td>
</tr>
<tr>
<td>Meningoencephalitis</td>
</tr>
<tr>
<td>Parkinson Dz</td>
</tr>
<tr>
<td>TBI</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
</tr>
</tbody>
</table>

--Modified from Chin JH et al, Neurology 2014

UCLA Stroke Center
Acute Stroke Care 1990
Therapies with FDA Approval or Positive Trials

- Ischemic Stroke
  - None
- Intracerebral Hemorrhage
  - None
- Subarachnoid Hemorrhage
  - Nimodipine
- Intraventricular Hemorrhage
  - None
Ischemic Stroke
- Stroke Unit Care
- PO Aspirin < 48 hrs
- IV TPA < 3 hrs
- IV TPA 3–4.5 hrs
- IA fibrinolysis < 6 hrs
- IA stent retrievers < 8 hrs
- IA aspiration devices < 8 hrs
- Endovascular temperature control

Intracerebral Hemorrhage
- Stroke Unit Care
- Endovascular temperature control

Subarachnoid Hemorrhage
- Stroke Unit Care
- GDC coil, Matrix coil, stent assisted coiling
- Endovascular temperature control
- Nimodipine
- IA angioplasty for vasospasm

Intraventricular Hemorrhage
- Intraventricular TPA and drainage
- Endovascular temperature control
When all you have is a hammer, everything looks like a nail.
When all you have is a hammer, everything looks like a nail.
Treatments that Work
The Challenge of Mapping the Responder Population

The “Hype Cycle”
of New Technologies
(and New Treatments)
Treatments that Work
The Challenge of Mapping the Responder Population

People react differently to drugs

“One size does not fit all…”

Patient population with same disease phenotype

Ethnicity
Age
Pregnancy
Genetic factors
Disease
Drug interactions

Toxic responders
Non-responders
Responders

Patients with drug toxicity

Patients with non-response to drug therapy

Patients with normal response to drug therapy

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Variable Types that May Distinguish Neurologic Responders and Nonresponders

- **Continuous**
  - Age
  - Multiple neurologic diseases
- **Time**
  - Acute ischemic stroke
  - Alzheimer (pre, early, late)
  - Parkinson (pre, early, late)
  - Migraine (Abortive vs symptomatic relief)

- **Ordinal**
  - Disease stage
  - Multiple sclerosis (single episode, relapsing-remitting, progressive)
  - Parkinson (stages 1-5)
  - Status epilepticus (5 electrographic stages)

- **Categorical**
  - Seizures (focal, tonic-clonic, absence, atonic, etc)
  - Myotonic dystrophy (type 1 and type 2)

- **Multivariate**
  - Genomic classifier panels
  - Combination of any of above

*UCLA Stroke Center*
The Ischemic Penumbra

Core Infarct

Ischemic Penumbra:
zone of salvageable tissue surrounding core infarct
In a typical acute ischemic stroke, every minute the brain loses

- 1.9 million neurons
- 14 billion synapses
- 7.5 miles myelinated fibers

-- Saver, Stroke 2006
A Drop of Brain (1cc), A Week of Healthy Life
Quality Adjusted Life-Years (QALYs)

- Early REPERFUSION + Total PENUMBRA SALVAGE
- Late REPERFUSION + Little PENUMBRA SALVAGE

Penumbra (yellow) and core (blue) volumes on perfusion CT pre-tPA

Final infarct volume on 24h MRI

DALYs = YLD (Years Lived with Disability) + YLL (Years of Life Lost)

Pre-stroke
First 3m post-stroke
> 3m post-stroke

--Saver, Brain Brain 2017
--Kawano et al, Brain 2017
Mechanical Thrombectomy for Acute Ischemic Stroke

Stent Retriever
Aspiration Catheter

UCLA Stroke Center
HERMES: Era of Highly Effective Reperfusion Therapy
Time from Onset to Expected Puncture Odds of Reduced Disability with EVT vs Medical

Common Odds Ratio Using 6-Level mRS

Time From Symptom Onset to Expected Arterial Puncture, min

7.3 hrs

Time from Onset to Expected Puncture Odds of Reduced Disability with EVT vs Medical

Benefit Per Hundred

Common Odds Ratio Using 6-Level mRS

Favors endovascular thrombectomy

Favors medical therapy alone

7.3 hrs

Time From Symptom Onset to Expected Arterial Puncture, min

Fast and Slow Progressors
Collateral Variability

Strategies to Identify LVO Patients with Salvageable Ischemic Penumbra

Hyperacute therapy when nearly all patients have penumbra

Imaging required to assess pathophysiology

% Patients with Penumbra

Time From Onset (Hours)

< 6 Hrs

> 6 Hrs
Bioenergetic Compromise

Hemodynamic Compromise

Occlusions or Stenoses

Tissue Status
CBV CT

Perfusion Status
PCT

Vessel Status
CTA

Multimodal CT

Multimodal MRI

DWI

PWI

MRA

Bioenergetic Compromise

Hemodynamic Compromise

Occlusions or Stenoses
Potential Populations for Thrombectomy: Example of Time

<table>
<thead>
<tr>
<th>Mismatch</th>
<th>0-3h</th>
<th>3-6h</th>
<th>6-7h</th>
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<th>8-12h</th>
<th>12-16h</th>
<th>16-20h</th>
<th>20-24h</th>
<th>&gt;24h</th>
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</thead>
<tbody>
<tr>
<td>Not performed</td>
<td>green</td>
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<td>150-199%</td>
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Trial Design Options for Expanding Eligible Patients

- Incremental expansion
  » From “sweet spot” out
  » Series of trials or adaptive expansion
- Broad enrollment
  » Wide entry criteria with enroll all or uncertainty principle
  » Single trial or adaptive reduction
Distinctive Aspects of Neurology Clinical Trials

- Complex biology
  - High rate of trial non-positivity/drug failure
    - 99.6% of Alzheimer disease trials nonpositive
    - JLS – 3/125 (.024)

- Disability in addition to mortality
  - Ordinal end point analysis and interpretation
  - Continuous end point development
    - Item response banks
    - MCID challenge

- Cognitive impairment of the subject
  - Patient-centered outcomes require proxy reporting
  - Informed consent challenges
    - Acute – EFIC; Chronic – consent as a continuum
How Diseases Affect Persons

- **Biologic**
  - Anatomy and physiology
- **Functional**
  - Physical, cognitive, and affective capabilities
- **Social**
  - Role in family and society
- **Experiential**
  - Subjective experience
The Most Appropriate Outcome Measure

- The composite of all the outcomes the treatment might alter, in proportion to the degree they are valued by the patient
Outcome Measures for Clinical Trials in Neurology

• Binary
  » Advantages: simple to analyze and interpret
  » Disadvantages: reduced power, misses important effects
  » Example: Survival – ALS, Brain Tumor

• Ordinal
  » Advantages: covers wide range of effects, increased power (nonparametric)
  » Disadvantages: challenging to analyze and interpret
    • Examples: Survival – ALS, Brain Tumor
    • Spasticity – Ashworth Scale
    • Multiple Sclerosis – Expanded Disability Status Scale
    • TBI – Glasgow Outcome Scale
    • Stroke – modified Rankin Scale
    • Parkinson – Hoehn and Yar Scale

• Continuous
  » Advantages: covers full range, greatest power (parametric)
  » Disadvantages: challenging to derive; can detect non-meaningful change (below MCID)
    • Examples: Walking speed
    • Generic health QoL: SF36.
    • Neurologic disorder QoL: Neuro-QoL
    • Disease-specific QoL: QUEST (essential tremor)
    • Disability: AMC Linear Disability Scale

UCLA Stroke Center
# Modified Rankin Scale

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms</td>
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</table>
| 1     | No significant disability  
         --able to perform all usual activities |
| 2     | Slight disability  
         --able to look after own affairs |
| 3     | Moderate disability  
         --requires some help, but able to walk unassisted |
| 4     | Moderately severe disability  
         --assistance needed for walking and bodily needs |
| 5     | Severe disability  
         --bedridden, requires constant nursing care |
| 6     | Dead          |
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Innovative Approaches to Two Major Challenges in the Design of Pivotal Neuroclinical Trials

Roger J. Lewis, MD
Vice-Chair and Professor of Emergency Medicine, DGSOM at UCLA

NINDS Clinical Trial Methodology Course Keynote
A New Day DAWNS

Jeffrey L. Saver, MD,
SA Vice-Chair and Professor of
Neurology, DGSOM at UCLA

NINDS Clinical Trial Methodology Course Keynote
DAWN in Full Daylight

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

Tudor G. Jovin MD & Raul G. Nogueira MD
on behalf of the DAWN investigators
**Study Objective**

To demonstrate superior functional outcomes at 90 days with Trevo plus medical management compared to medical management alone in appropriately selected patients treated six to 24 hours after last seen well.

**Study Design**

<table>
<thead>
<tr>
<th>Study design</th>
<th>Global, multi-center, adaptive, population enrichment, prospective, randomized, open, blinded endpoint (PROBE), controlled FDA IDE trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient population</td>
<td>• Acute ischemic stroke (AIS) with large vessel occlusion&lt;br&gt;• Able to be randomized between six to 24 hours after time last known well&lt;br&gt;• Clinical imaging mismatch (CIM) defined by age, core, and NIHSS</td>
</tr>
<tr>
<td>Target vessel</td>
<td>Intracranial ICA, M1 segment of the MCA</td>
</tr>
<tr>
<td>Randomization</td>
<td>1:1 Trevo + medical management vs. medical management alone</td>
</tr>
<tr>
<td>Sites</td>
<td>Up to 50 sites worldwide (30 US and 20 international)</td>
</tr>
<tr>
<td>Sample size</td>
<td>500 maximum subjects: 250 in the treatment arm and 250 in the control arm. Minimum sample size is 150 subjects.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>24 hours (-6/+24), day 5-7/discharge, day 30 (± 14), and day 90 (± 14)</td>
</tr>
</tbody>
</table>
Study Methods: Workflow

NCCT/DWI:
<1/3 MCA Territory

CTA/MRA:
ICA-T and/or MCA-M1
(Tandem Occlusions Allowed)

RAPID CTP/DWI CIM:
A. ≥80 y/o:
   1. NIHSS ≥10 + core <21cc
   2. NIHSS ≥10 + core <31cc
   3. NIHSS ≥20 + core <51cc
B. <80 y/o:
   1. NIHSS ≥10 + core <21cc

1:1 Randomization:
- CIM subgroup
- ICA-T vs M1
- 6-12 vs 12-24h

Control
90-day mRS
- U-W mRS
- mRS 0-2
Thrombectomy
## Study endpoints

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>90-day disability assessed by the modified Rankin scale (mRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Assessed via <strong>Utility-Weighted mRS</strong></td>
</tr>
<tr>
<td></td>
<td>- Nested <strong>Dichotomous mRS 0-2</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary endpoints</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- &quot;Early response&quot; at day 5-7/discharge, defined as a NIHSS drop of ≥10 points from baseline or NIHSS score 0 or 1</td>
</tr>
<tr>
<td></td>
<td>- All cause mortality rates</td>
</tr>
<tr>
<td></td>
<td>- Median final infarct size at 24 (-6/+24) hours from randomization</td>
</tr>
<tr>
<td></td>
<td>- Revascularization rates at 24 (-6/+24) hours from randomization</td>
</tr>
<tr>
<td></td>
<td>- Treatment arm: reperfusion rates post device and post procedure by angiography core lab measurement of modified TICI &gt; 2b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary safety endpoint</th>
<th>Stroke related mortality at 90 days</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Secondary safety endpoint</th>
<th>Incidence of SICH, by ECASS III definition, within 24 (-6/+24) hours post randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence of neurological deterioration from baseline NIHSS score through day 5-7/discharge</td>
</tr>
<tr>
<td></td>
<td>Incidence of procedure-related and device-related serious adverse events through 24 (-6/+24) hours post randomization</td>
</tr>
</tbody>
</table>
TRIAL ENROLLMENT RATE AND TERMINATION

<table>
<thead>
<tr>
<th>Site Status</th>
<th>Actual Subjects</th>
<th>Planned Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sites Qualified</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td>Sites Initiated</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>IRB/EC Approvals</td>
<td>31</td>
<td>206</td>
</tr>
</tbody>
</table>

Actual / Projected Enrollment

Enrollment stopped at DSMB recommendation.

*Boundary for first enrichment not crossed.*
Results

CBF (<30%) volume: 2.0 ml
Perfusion (Tmax>6.0s) volume: 100.0 ml
Mismatch volume: 98.0 ml
Mismatch ratio: 50.0

This image is not intended for primary diagnosis
Randomization and follow-up

Randomized (n=206)

Trevo + MM N=107
- Final FU available
  106 90-day complete
  1 withdrew after 30 day visit*

Stratification by clinical core mismatch, time, and occlusion location

MM N=99
- Final FU available
  96 90-day complete
  2 LTFU after 30 days*
  1 withdrew after 30 day visit*

* 30 day mRS carried forward in 4 pts
100% follow-up to 30 days
## Demographics

<table>
<thead>
<tr>
<th></th>
<th>Treatment arm N=107</th>
<th>Control arm N=99</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (median, [IQR])</td>
<td>72.0 [60.0-79.0]</td>
<td>73.0 [61.0-82.0]</td>
<td>0.51</td>
</tr>
<tr>
<td>NIHSS, baseline (median, [IQR])</td>
<td>17 [13-21]</td>
<td>17 [14-21]</td>
<td>0.64</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>39.3%</td>
<td>51.5%</td>
<td>0.09</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>66.0%</td>
<td>63.6%</td>
<td>0.77</td>
</tr>
<tr>
<td>Black or African American</td>
<td>21.7%</td>
<td>15.2%</td>
<td>0.28</td>
</tr>
<tr>
<td>Other*</td>
<td>12.3%</td>
<td>21.2%</td>
<td>0.09</td>
</tr>
<tr>
<td>IV-tPA administered</td>
<td>4.7%</td>
<td>13.1%</td>
<td>0.05</td>
</tr>
</tbody>
</table>

* Inclusive of Asians and International sites that did not disclose race per local authorities
Patient presentation

<table>
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<th>Time since time last seen well to randomization (hrs)</th>
<th>Treatment arm N=107</th>
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<th>P- value</th>
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<tr>
<td>Mean ± SD</td>
<td>13.4 ± 4.1</td>
<td>13.0 ± 4.5</td>
<td>0.53</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>12.2 (10.2, 16.0)</td>
<td>13.2 (9.4, 15.8)</td>
<td></td>
</tr>
<tr>
<td>Range (min, max)</td>
<td>(6.1, 23.5)</td>
<td>(6.4, 23.9)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stroke sub-population</th>
<th>Treatment arm N=107</th>
<th>Control arm N=99</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wake up stroke</td>
<td>64.5%</td>
<td>47.5%</td>
<td>0.01</td>
</tr>
<tr>
<td>Witnessed stroke</td>
<td>10.3%</td>
<td>14.1%</td>
<td>0.52</td>
</tr>
<tr>
<td>Un-witnessed stroke</td>
<td>25.2%</td>
<td>38.4%</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Co-primary endpoints

<table>
<thead>
<tr>
<th></th>
<th>Trevo</th>
<th>MM</th>
<th>Treatment benefit (95% CI)</th>
<th>Bayesian probability of superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 90 weighted mRS</td>
<td>5.5 ± 3.8</td>
<td>3.4 ± 3.1</td>
<td>2.1 (1.20, 3.12)</td>
<td>&gt;0.9999*</td>
</tr>
<tr>
<td>Day 90 mRS (0-2)</td>
<td>48.6%</td>
<td>13.1%</td>
<td>35.5% (23.9%, 47.0%)</td>
<td>&gt;0.9999*</td>
</tr>
</tbody>
</table>

NNT for 90-day functional independence = 2.8

*Similar to p<0.0001
Primary outcome

TREVO:
- mRS 0/uW mRS 10: 9%
- mRS 1/uW mRS 9.1: 17%
- mRS 2/ uW mRS 7.6: 13%
- mRS 3/ uW mRS 6.5: 13%
- mRS 5-6/ uW mRS 0: 26%

CONTROL:
- mRS 0/uW mRS 10: 4%
- mRS 1/uW mRS 9.1: 16%
- mRS 2/ uW mRS 7.6: 34%
- mRS 3/ uW mRS 6.5: 36%

Probability of superiority >0.9999

73% relative risk reduction of dependency in ADL’s NNT for any lower disability 2.0
## 90 Day mRS 0-2 by TLSW to Randomization

<table>
<thead>
<tr>
<th></th>
<th>Trevo</th>
<th>MM</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-12h</td>
<td>55.1%</td>
<td>20.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12-24h</td>
<td>43.1%</td>
<td>7.4%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

![Graph showing estimated probability over time since last seen well to randomization (hrs)](image)
Secondary effectiveness endpoints

Pre and 24 hour median core size

- Pre
- 24 Hours

P = 0.02

NIHSS early responders

P < 0.001

47.7% improvement

19.2%
Conclusions

- Thrombectomy with Trevo in DAWN-eligible patients is associated with improvement in clinical outcomes across the entire range of utility weighted mRS and with higher rates of functional independence (mRS 0-2) compared to standard medical therapy (48.6% vs 13.1%, probability of superiority >0.999, NNT = 2.8)

- The treatment effect size in DAWN is the highest out of any stroke trials to date and suggests that the presence of Clinical-Core Mismatch is a critical predictor of treatment effect independent of time to presentation

- Treatment effect persisted throughout 24 hours from TLKW; however, earlier treated patients do better

- Thrombectomy with the Trevo device in patients presenting beyond 6 hours of TLSW had comparable safety profile to thrombectomy performed within 6 hours
Potential Populations for Thrombectomy: Examples of Time and Penumbra

<table>
<thead>
<tr>
<th>Mismatch</th>
<th>0-3h</th>
<th>3-6h</th>
<th>6-7h</th>
<th>7-8h</th>
<th>8-12h</th>
<th>12-16h</th>
<th>16-20h</th>
<th>20-24h</th>
<th>&gt;24h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not performed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;200%</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>150-199%</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>100-149%</td>
<td>✔</td>
<td></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>50-99%</td>
<td></td>
<td></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>20-49%</td>
<td></td>
<td></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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</tr>
</tbody>
</table>
It's a new DAWN!

Thank you
to patients, families and all investigative sites