Intravenous Thrombombolysis in Stroke Patients with Unknown Time of Onset –
Results of the Multicentre, Randomized, Double-blind, Placebo-Controlled WAKE-UP Trial

Disclosures

- WAKE-UP has received funding by the European Union Seventh Framework Programme
- There was no industry funding or involvement in any aspect of the trial
Aim and Design

- **Aim**: To prove efficacy and safety of MRI-based thrombolysis in patients with unknown time of symptom onset
- **Design**: randomised, placebo-controlled clinical trial (Alteplase vs. Placebo 1:1)
- **Planned sample**: 800 ischemic stroke patients (unknown symptom onset)
- **Inclusion criteria**:
  - Acute stroke with unknown symptom onset, disabling neurological deficit
  - Last known well >4.5 hours (ie not eligible for IV alteplase by licence)
  - Age 18-80 years
  - Treatment can be started within 4.5 h of symptom recognition
  - Written informed consent
  - MRI completed and indicative of lesion age ≤4.5 h: “DWI-FLAIR-mismatch”
- **Exclusion criteria**:
  - Planned thrombectomy
  - Any contraindication against treatment with alteplase (except for unknown time window)
Study Procedures and Results

- **Randomization:** Randomization in 1:1 ratio (alteplase or placebo), stratified according to age (≤60 / >60 years) and symptom severity (NIHSS score ≤10 / >10)

- **Treatment:** Alteplase 0.9 mg per kilogram of body weight (with 10% as bolus, the remainder by infusion over 60 minutes) or matching placebo

- **Follow-up:** MRI at 22-36 hours to detect intracranial hemorrhage and to assess infarct volume; Clinical follow-up at 22-36 hours, 5-9 days, and 90 days after stroke

- **End of the trial:** Enrolment stopped on June 30, 2017 at Steering Committee decision based on anticipated cessation of funding from the European Union

- **503 patients were randomized:** 254 assigned to receive alteplase and 249 to receive placebo
Primary Endpoint

Score on the Modified Rankin Scale at 90 Days

- **Alteplase**: 53.3% in 0-1 category and 46.7% in 2-6 category
- **Placebo**: 41.8% in 0-1 category and 58.2% in 2-6 category

### Endpoint: Favorable outcome (mRS 0-1) at 90 days

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Alteplase (n=254)</th>
<th>Placebo (n=249)</th>
<th>Effect Variable</th>
<th>Adjusted Value (95% CI) *</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable outcome (mRS 0-1) at 90 days</td>
<td>131/246 (53.3%)</td>
<td>102/244 (41.8%)</td>
<td>Odds ratio</td>
<td>1.61 (1.09-2.36)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* *Adjusted for age and NIHSS at baseline*
### Selected Secondary and Safety Outcomes

- **Secondary efficacy endpoint: mRS “shift analysis”**

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<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median mRS score at 90 days (“shift analysis“)</td>
<td>1 (1-3)</td>
<td>2 (1-3)</td>
<td>Common odds ratio</td>
<td>1.62 (1.17-2.23)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

- **Safety endpoints:**

<table>
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<tr>
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<th>Placebo</th>
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<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death at 90 days</td>
<td>4.1%</td>
<td>1.2%</td>
<td>3.38 (0.92-12.52)</td>
<td>0.07</td>
</tr>
<tr>
<td>Symptomatic intracranial hemorrhage as defined in SITS-MOST</td>
<td>2.0%</td>
<td>0.4%</td>
<td>4.95 (0.57-42.87)</td>
<td>0.15</td>
</tr>
<tr>
<td>Parenchymal hemorrhage type 2 (PH-2)</td>
<td>4.0%</td>
<td>0.4%</td>
<td>10.46 (1.32-82.77)</td>
<td>0.03</td>
</tr>
<tr>
<td>Any serious adverse event (SAE)</td>
<td>22.3%</td>
<td>21.3%</td>
<td></td>
<td>0.83</td>
</tr>
</tbody>
</table>

* Adjusted for age and NIHSS at baseline
Conclusions

- In patients with unknown symptom onset stroke with MRI pattern of DWI-FLAIR-mismatch, treatment with alteplase resulted in better functional outcome than placebo.
- Consistent benefit across all categories of outcome and major clinical secondary endpoints.
- Effect size of MRI-guided thrombolysis in unknown symptom onset stroke is comparable to effect size of thrombolysis <4.5 hours.
- Numerically higher rates of symptomatic intracranial hemorrhage and trend towards higher mortality with alteplase, which might have become significant with larger sample size.
- Paradigm change: first positive trial of intravenous thrombolysis relying on patients selection by advanced brain imaging without information on time of symptom onset.
- MRI-guided intravenous thrombolysis represents an effective treatment option for stroke patients with unknown symptom onset, especially for those with minor or moderate stroke who are not eligible for mechanical thrombectomy.
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