Publishable summary

Project title: Efficacy and safety of MRI-based thrombolysis in wake-up stroke: a randomised, double-blind, placebo-controlled trial (WAKE-UP)

Website: www.wakeup-stroke.eu

Contractors involved (WAKE-UP Consortium):

The project is coordinated by Prof. Christian Gerloff (Partner 01, UKE) Universitätsklinikum Hamburg-Eppendorf, Martinistraße 52, 20246 Hamburg, Germany.

Other partners and team leaders:

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- Partner 04: IDIBGi, Institut d'Investigació Biomèdica de Girona Doctor Joseph Trueta, Spain
- Partner 05: KUL, Katholieke Universiteit Leuven, Belgium
- Partner 06: HCL, Hospices Civils de Lyon, France
- Partner 07: UG, University of Glasgow, United Kingdom
- Partner 08: SAFE, Stroke Alliance for Europe, Belgium
- Partner 09: FME, Fraunhofer-Gesellschaft zur Förderung der Angewandten Forschung e.V., Germany
- Partner 10: mediri, Medical Imaging Research Institute, Germany
- Partner 11: ZytoService Deutschland GmbH, Germany
- Partner 12: GABO:mi Gesellschaft für Ablauforganisation :milliarium mbH & Co. KG, Germany
- Partner 13: ORION Clinical Services Ltd, United Kingdom

1.1 Summary description of project context and objectives

WAKE-UP is an investigator-initiated, multicentre, randomized, double-blind, placebo-controlled trial designed to test efficacy and safety of MRI-based intravenous thrombolysis in patients with wake-up stroke. Stroke is a devastating disease with massive social and economic impact. Every year 1.5 million patients suffer a stroke in the EU. Intravenous thrombolysis with recombinant tissue plasminogen activator (Alteplase) is the only effective and approved specific treatment for acute ischemic stroke. However, thrombolysis relies on information about the time of symptom onset as it was only demonstrated to be effective and safe within 4.5 hours of symptom onset. Up to 20% of stroke patients wake up with stroke symptoms and information on time of symptom onset is not available in these patients. Thus, these patients are currently excluded from thrombolysis. The aim of WAKE-UP is to provide treatment options for these patients.

Recently it was demonstrated that MRI carries the potential to identify patients likely to be within a time-window for thrombolysis (≤4.5 hours) by a specific MRI pattern, i.e. the mismatch between a visible lesion on diffusion weighted imaging (DWI) and a normal fluid attenuated inversion recovery (FLAIR) image. WAKE-UP will use this technique to randomise patients waking up with stroke symptoms to either treatment with Alteplase or placebo. A total of 800 patients will be randomized in 60 centres in six European countries. The main objectives of WAKE-UP are:

To change clinical practice and to improve the treatment of acute ischemic stroke

WAKE-UP is designed to provide unquestionable evidence for efficacy and safety of MRI based thrombolysis in wake-up stroke patients enabling specific treatment recommendations for acute stroke patients with unknown symptom onset.

To promote a paradigm-change in acute stroke treatment by translating research into clinical practice

Currently, acute stroke treatment critically depends on knowledge of the time point of symptom onset. WAKE-UP will promote a paradigmartic change in patient selection by using novel imaging techniques that hold the promise to identify patients likely to benefit from thrombolysis even if time of symptom onset is unknown.

To enhance the understanding of and optimise multiparametric imaging criteria for patient selection for acute stroke treatment

WAKE-UP will also study the potential impact of other novel imaging strategies such as penumbral imaging and vessel status in response to thrombolysis and by this help in optimizing multiparametric imaging criteria for patient selection for reperfusion treatment.

To provide a tool for the easy integration of modern imaging in acute treatment decisions in daily practice

WAKE-UP will provide a pipeline for the transfer of expert knowledge in acute stroke imaging to a larger number of stroke centres including software tools for image analysis training and computer assisted image processing.

To increase the competitiveness of European stroke research

Bringing together a consortium of renowned stroke researchers with innovative SMEs and enterprises WAKE-UP will set the ground for outstanding power to compete on the highest level in the international competition of stroke research and boost the innovative capacity of European health-related industries..

1.2 Work performed since the beginning of the project and the main results achieved so far

During the fourth reporting period activation of new trial sites and patient enrolment into the clinical trial were the main tasks. This was done successfully, the planned number of sites has been reached, and patient enrolment is speeding up. Development of the software tool for computer assisted image analysis (WP07) was finished.

WP01: Set-up framework

The trial infrastructure has proven effective during the fourth reporting period. All tasks of WP01 have been successfully completed by the end of the third reporting period.

WP02: Define imaging standards, training

The largest part of activities in WP02 has been completed. The tools for image training and certification are used effectively. By November 30 2015, 368 investigators have completed the image analysis training and certification.

WP03: Clinical trial

The number of active sites was increased according to the contingency plan deployed in the third reporting period and enrolment rates have steadily increased. By November 30 2015, 57 sites were active, and 919 patients were enrolled in WAKE-UP with 339 patients randomized and 580 screen failures (see Figure 1).

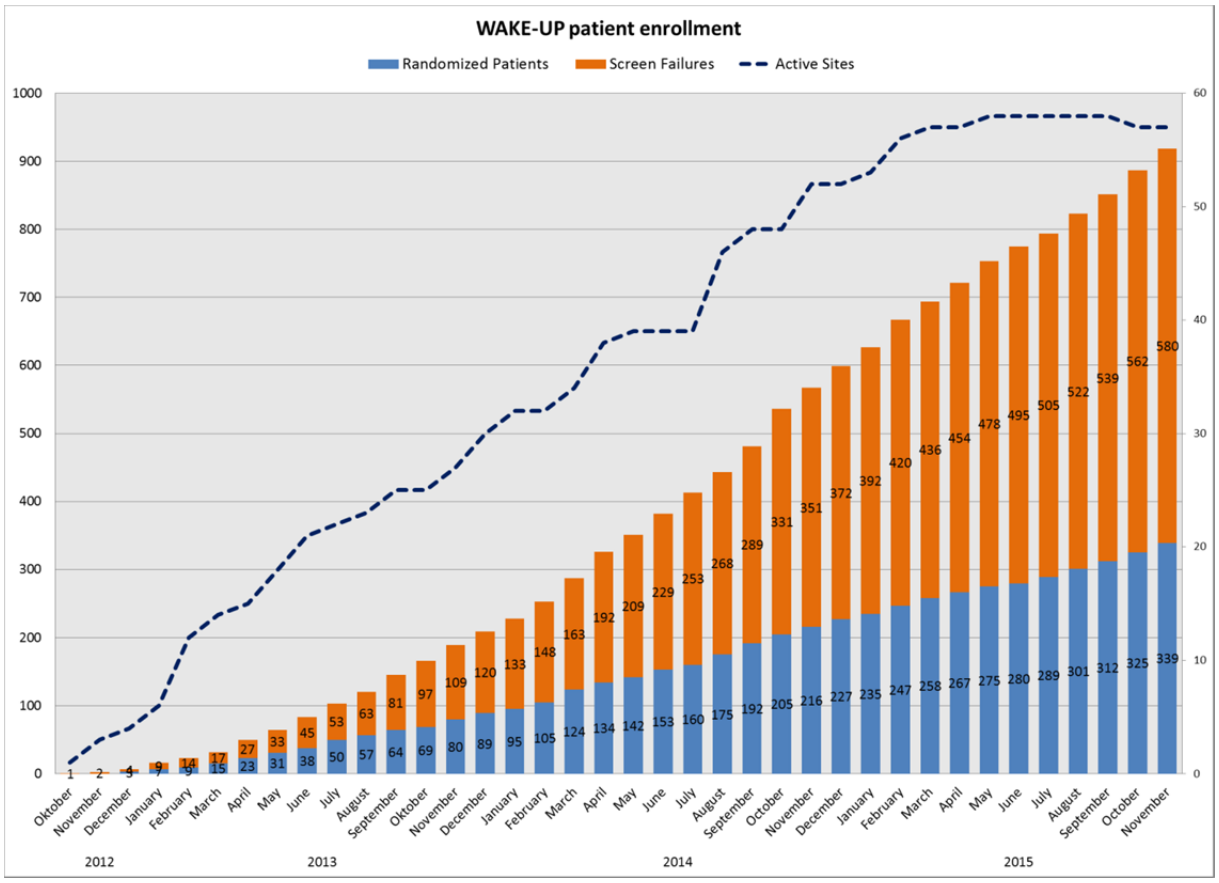

Figure 1: Active sites, patient enrolment, and patient randomization by the end of the 4th reporting period (30 November 3015)

The General Assembly decided to request a cost-neutral extension of the WAKE-UP project for additional 12 months in order to be able to successfully complete the clinical trial. In addition, extension of the trial to new countries was decided increasing the number of active study sites to 75-80.

WP04: Data and safety monitoring, ethics

The DSMB met two times, first to evaluate the results of the second safety interim analysis, and second to evaluate trial data of the third year. There were no safety issues of concern. The third Development Safety Update Report (DSUR) was prepared and submitted to the corresponding ethics committees and competent authorities.

WP05: Central image reading

The central image reading process by the Central Image Reading Board (CIRB) is running effectively. Overall, until the end of the forth reporting period, 1861 of 1942 cases (96%) were reviewed. Feedback is given to the local investigators in cases of disagreement referring to imaging inclusion and exclusion criteria.

WP06: Data management, statistics

The second interim safety analysis was performed according to the protocol after 200 patients had completed the trial. There were no safety concerns. Data for the third Development Safety Update Report (DSUR) for data evaluation by the DSMB were prepared.

WP07: Optimise image processing and software development

User-friendly image processing and analysis software is ready for distribution.

WP08: Multiparametric MRI and treatment response

Further proposals for scientific analyses to be performed within WP08 were discussed. A database and dedicated workflow for image data access and for further scientific analysis was finalised. All available MR images have been checked for quality and completeness.

WP09: Dissemination, transfer, scientific data sharing

The WAKE-UP website (http://www.wakeup-stroke.eu) is kept up to date presenting content tailored to each partner country including videos and written information in their local language giving a brief introduction and overview of WAKE-UP for both clinicians and members of the public. Regular updates on activities and enrolment progress are published.

1.3 The expected final results and their potential impact and use (including the socio-economic impact and the wider societal implications of the project so far)

WAKE-UP addresses a massive and growing health problem in the EU and will provide a manifest benefit for individual patients, doctors involved in the management of stroke, and the society at large. Stroke is the 2nd most common single cause of death and the most frequent cause of permanent disability in industrialised countries. Estimated 2 million people per year are hospitalized for stroke in the EU, including estimated 400.000 people with wake-up stroke. WAKE-UP will provide effective treatment options to large numbers of patients currently excluded from any specific acute stroke treatment. The clinical trial represents the core of the project. This trial is designed to provide evidence of efficacy and safety of MRI-based thrombolysis in stroke patients with unknown time of symptom onset. By this, WAKE-UP will provide an effective treatment for a large group of patients currently condemned to the natural course of the disease.

The results of WAKE-UP are expected to change guidelines of acute stroke management. We expect a positive trial to lead to an immediate change of clinical practice in stroke centres across the EU. We estimate that 100.000 patients with wake-up stroke per year are potentially eligible for thrombolysis. Many survivors of stroke lose their ability to work or live independently resulting in severe personal and societal losses. Based on the observed treatment effect in previous stroke thrombolysis trials we expect thrombolysis to result in a 10% absolute increase of patients surviving stroke with no or only minimal neurological symptoms and about 30% of patients with improved clinical outcome as an effect of thrombolysis. Thus, WAKE-UP might help avert lasting neurological symptoms or disability in estimated more than 10.000 patients per year in the EU. The overall effect on outcome across all outcome ranges will even be larger.

Being the most frequent reason for adult onset disability, stroke accounts for an enormous socio-economic burden. The economic costs of stroke add up to more than € 34 billion in the EU in 2006. By reducing the number of disabled patients after stroke, the results of WAKE-UP will lead to a tangible decrease of follow-up costs of stroke.

WAKE-UP will also contribute to harmonisation and standardisation of acute stroke treatment across the EU. Software for computer assisted image processing and analysis made available by WAKE-UP will help utilize and further spread this technology even beyond centres with special stroke imaging expertise. This will help to make the availability of best practice independent from pre-existing research activities and thus stimulate the implementation of best practice incorporating novel imaging standards in all Member States.

Additional MRI information such as vessel occlusion or perfusion lesion will not be used for enrolment but will be studied as possible modifiers of the response to thrombolysis. The results of WAKE-UP will encourage future research involving acute stroke treatment guided by multiparametric stroke MRI. Analysis of imaging predictors of outcome in WAKE-UP will likely ignite subsequent studies. Pre-planned pooled analysis with other MRI-based stroke trials will entail additional insights and further strengthen cooperation between European and international stroke research groups. This will set grounds for potential subsequent international investigator initiated clinical trials involving novel imaging techniques or novel drugs.

The trial is accompanied by activities increasing the awareness for acute stroke in the public and results will be disseminated within the scientific community as well as within the public. WAKE-UP will promote a paradigm-change in acute stroke treatment, and to provide effective treatment to a large new group of patients.