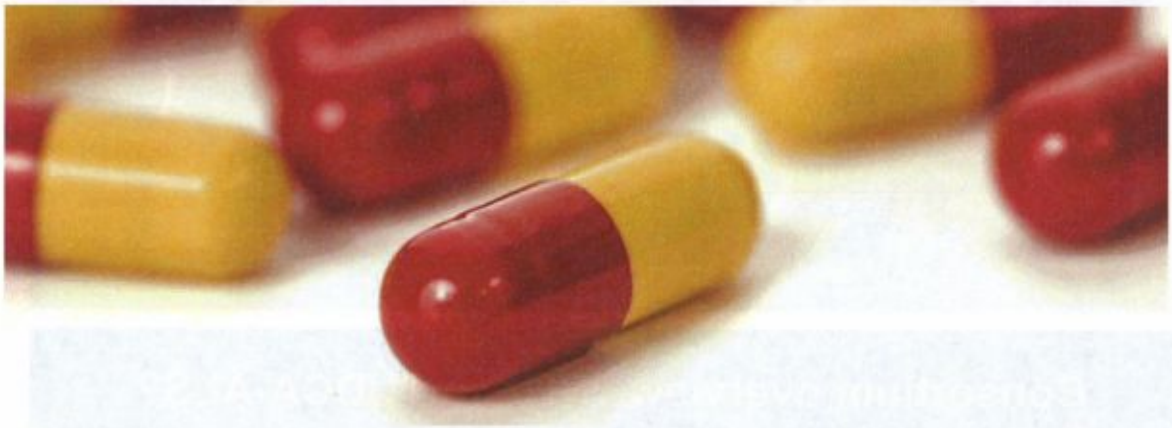
Meet the team in Italy! View in browser

TUDCA ALS

Newsletter #1
September 2019



Welcome to the first TUDCA-ALS newsletter

In this edition you will be able to meet the TUDCA-ALS team in Italy, read more about the recruitment of our first participant and find the answers to some of your frequently asked questions. I look forward to sharing news and progress of the TUDCA-ALS clinical trial in future editions of our newsletter.

Prof Alberto Albanese
TUDCA-ALS Study Co-ordinator

In this issue, you can read about:

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Consortium overview: What is TUDCA-ALS?

Amyotrophic lateral sclerosis (ALS) is a chronic non-communicable neurodegenerative disease, affecting 40,000 individuals in Europe and causing around 11,000 deaths each year. Although much has been achieved in understanding ALS disease complexity over the last two decades, there is still a pressing need to find disease-modifying therapies that slow disease progression.

TUDCA-ALS is a consortium involving researchers from seven countries in Europe, that aims to assess the safety and efficacy of **tauroursodeoxycholic acid** (also known as TUDCA) as add-on treatment in patients affected by ALS. The study will take advantage of the results of a proof-of-concept / proof-of-mechanism phase IIb study, showing that TUDCA delays the degeneration of motor neurons, allowing for longer survival of people living with the disease.

TUDCA-ALS embarked on its four-year collaborative journey to conduct this new phase III clinical trial on TUDCA in January 2018 and is supported by a grant provided by the **European Commission's Horizon 2020** Research and Innovation programme.

The project is coordinated by **Humanitas Research Hospital** (Italy) and brings together a team of excellence that includes leading clinicians, research scientists and laboratories from the **Universität Ulm** (Germany), the **University of Sheffield** (United Kingdom), the **Centre Hospitalier Regional Universitaire de Tours** (France), the **Katholieke Universiteit Leuven**

(Belgium), the **Universitair Medisch Centrum Utrecht** (Netherlands) and the **Trinity College Dublin** (Ireland).

These centres are working closely with **Bruschettini Srl** (Italy), the marketing authorisation holder of the pharmaceutical product, **Istituto Superiore di Sanità** (Italy), the leading technical-scientific body of the Italian National Health System, and the **Motor Neurone Disease Association** (United Kingdom), one of the biggest ALS/MND charities in Europe.

You can find out more about the study and how to take part at the **TUDCA-ALS website**.

TUDCA-ALS Consortium Partners

1 - **Humanitas Research Hospital** (ICH)
2 - **Universität Ulm** (UULM)
3 - **University of Sheffield** (USFD)
4 - **Centre Hospitalier Regional Universitaire de Tours** (CHUT)
5 - **Katholieke Universiteit Leuven** (KUL)
6 - **Universitair Medisch Centrum Utrecht** (UMCU)
7 - **Trinity College Dublin** (TCD)
8 - **Bruschettini Srl** (BRU)
9 - **Istituto Superiore di Sanità** (ISS)
10 - **Motor Neurone Disease Association** (MNDA)

Meet the Team - Italy

Partner 1 - Humanitas Research Hospital (ICH)

Humanitas Research Hospital, located in Rozzano (Milan), Italy, is the Coordinator of the TUDCA-ALS clinical trial.

Humanitas is a highly specialized general hospital recognised by the Italian Ministry of Health and Joint Commission International as a centre of excellence for the quality of healthcare services and for its ability to translate the results of research and innovation into everyday clinical practice. More than 300 researchers from 16 countries work in close collaboration with the 650 physicians of the hospital, in order to facilitate application of the most recent advances in healthcare through a systematic and ongoing process of innovation.

The Unit of Neurology at Humanitas Research Hospital employs a team of skilled neurologists dedicated to the diagnosis and treatment of several neurological diseases, including ALS.

The Humanitas Principal Investigator is the Director of the Neurology Unit, Professor Alberto Albanese. Humanitas' role in the project is:

- to develop essential study documents and to obtain ethical approvals;
- to recruit and follow up ALS patients;
- to assess biomarkers of disease and treatment on samples collected during the trial;
- to contribute to the dissemination and communication activities and to exploit project results;
- to coordinate Parties involved in the TUDCA-ALS project.

Humanitas has involved five additional clinical trial units in Italy to recruit study participants:

- **ALS Expert Center (CRESLA) of Turin:** CRESLA is a specialist ALS clinic that conducts research which involves approximately 400 patients affected by various forms of motor neuron diseases per year. CRESLA Director and Principal Investigator for the TUDCA-ALS trial in Turin is Professor Adriano Chiò.

- **Santa Maria University Hospital of Terni**: the Neurology Department at Terni University Hospital has specific clinical expertise in the field of neurodegenerative disorders, including ALS. Professor Carlo Colosimo, Chairman of the Neurology Department, is the Principal Investigator for the TUDCA-ALS trial in Terni.

- **NEuroMuscular Omnicenter (NEMO)**: NEMO is located within the Niguarda Hospital in Milan. Since 2008, NEMO has treated 1,600 patients with ALS, and has participated in a numerous clinical trials in ALS. The Principal Investigator involved in this trial is Doctor Christian Lunetta, responsible for care and research on ALS at NEMO Clinical Center.

- **IRCCS Istituto Auxologico Italiano**: the ALS Center at IRCCS Istituto Auxologico Italiano in Milan contributed to the definition of different international clinical guidelines

and has been a partner in several international consortia on ALS. Professor Vincenzo Silani, Director of the Neurology Unit and Stroke Unit, is the Principal Investigator for Auxologico.

- **AOU Università degli Studi della Campania**: the ALS Center at Università degli Studi della Campania in Naples is one of the main tertiary referral ALS Centers in the South of Italy. The Principal Investigator for the trial is the Director of the Center, Professor Gioacchino Tedeschi.

" I am excited to announce that the TUDCA-ALS clinical trial has recruited its first participant in Italy and I am looking forward to the trial rolling out across the European network of participating centres in the coming months."

Prof Alberto Albanese
TUDCA-ALS Study Co-ordinator

First participant has been recruited

TUDCA-ALS, a phase III clinical trial to determine whether TUDCA (tauroursodeoxycholic acid) in combination with riluzole can slow progression of ALS, has recruited its first study participant.

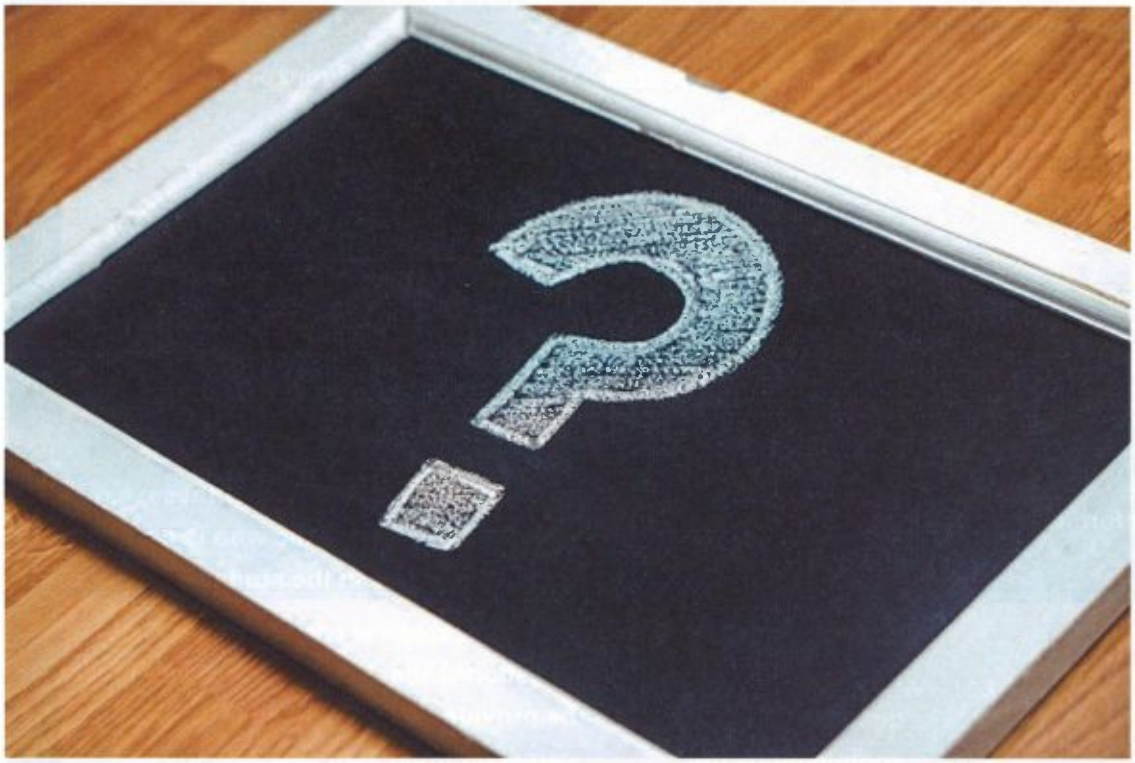
Professor Albanese says "I am excited to announce that the TUDCA-ALS clinical trial has recruited its **first participant** in Italy and I am looking forward to the trial rolling out across the European network of participating centres in the coming months."

The trial plans to recruit **440** participants across **7 countries in Europe** (Italy Germany, UK,

France, Belgium, Netherlands and Ireland) and will investigate a new possible treatment for ALS.

The current status of enrollments in all centres can be found below:

Centre	Number of patients enrolled	Number of patients randomised
IT01 - Rozzano	7	4
IT02 - Torino	0	0
IT03 - Terni	2	0
IT04 - Milano (NEMO)	8	2
IT05 - Milano (Auxologico)	8	3
IT06 - Napoli	4	0
DE01 - Ulm	4	0
DE02 - Berlin	0	0
DE03 - Essen	0	0
DE04 - Hannover	0	0
DE05 - Jena	0	0
DE06 - Dresden	0	0
UK01 - Sheffield	0	0
UK02 - Preston	0	0
UK03 - Salford	0	0
UK04 - Liverpool	0	0
UK05 - Plymouth	0	0
FR01 - Tours	2	0
FR02 - Limoges	0	0
FR03 - Montpellier	0	0
FR04 - Bordaeux	0	0
BE01 - Leuven	0	0
NL01 - Utrecht	0	0
IR01 - Dublin	0	0



Frequently Asked Questions

There are a number of questions that have been asked by sites during the set up of the TUDCA-ALS clinical trial and a selection of the most frequently asked questions are in the table below:

Topic	Question	Answer
Eligibility Criteria	When are inclusion and exclusion criteria assessed?	Inclusion criteria 1-5 and 7 are assessed at screening visit (month -3), while inclusion criterion 6 and all exclusion criteria are assessed up to month 0.
	Is "disease duration ≤ 18 months" considered from diagnosis of ALS or from the onset of symptoms?	Disease duration is considered from the onset of ALS symptoms.
	If a patient does not achieve a forced vital capacity ≥ 70% of normal at screening, is it	If the investigator believes that the test is not satisfactory for some reason, it is possible to repeat it.

	possible to repeat the test?	
Concomitant medications	Is treatment with riluzole allowed?	Yes, treatment with riluzole is an inclusion criteria.
	Is treatment with edaravone allowed?	No, edarovone is not allowed. To be recruited in the TUDCA-ALS trial, the patient needs to stop treatment with edaravone and wait 30 days before they can be recruited into the trial.
Informed consent	If the patient is unable to write, who can sign the informed consent form?	The informed consent form may be signed by an independent witness, e.g. someone from the clinic who is not directly involved in the study.
Questionnaires	If the patient is unable to write, can questionnaires be completed by the caregiver?	Yes, the caregiver can complete questionnaires. However, answers must be provided by the patient. The caregiver must sign and date the last page of the questionnaires, and affirm to be the patient's caregiver.
Visit schedule	How are visit dates calculated?	Visit dates for the lead-in period must be scheduled every six weeks, starting from the screening visit date (month -3). Visit dates for the double-blind period must be scheduled every three months, starting from the randomisation visit date (month 0).
	Is there a tolerance window for study visits?	Yes. Visit dates may be scheduled with a tolerance window of ±15 days for visits in the lead-in period, and ±30 days for visits in the double-blind period.
	Is it possible to split the visits over two days?	Yes, as long as this is feasible from a logistics point of view.
	When is the study medication dispensed to patients?	The study medication is first dispensed at month 0, following randomisation. As a rule, three monthly boxes should be dispensed at each visit. Therefore, the

		last three boxes should be dispensed at month 15.
Study drug dispensation	If a patient returns study medication supplies, is it possible to re-issue those drugs back to the patient?	No. Medication returned from the patient should be kept in the pharmacy for drug accountability and not re-issued to patients. The only exception is if four (instead of three) boxes of study drug have been dispensed (see below).
	If the tolerance window for visits in the double-blind period is ± 30 days, how should study medication be dispensed to cover for the maximum amount of time?	If it is known that the following visit might not be scheduled within three months, it is possible to dispense four boxes instead of three, provided that: 1. This is reported in the medical chart and in the dispensing form. 2. At the following visit, unused medication in the fourth box is returned by the patient and is re-dispensed to the patient.
Study drug administration	If the patient vomits after taking the study medication, is the drug to be re-administered?	No. In case of vomiting after taking the study drug, the patient should not take another dose until the next scheduled one.
	In case of diarrhea and subsequent dosage reduction from 2g to 1g daily, how many times does the patient have to take study medication.	In case of dosage reduction, study medication has to be administrated at the dose of 500mg twice daily.
Liver function exams	Liver function parameters must be monitored also at months 1 and 2, to assess drug safety. Since there are no visits foreseen in that period, would it be possible to perform these exams in another centre?	All exams should preferably be performed in the same centre. However, if the patient lives far away, the liver function exams scheduled for months 1 and 2 can be performed in another centre. The results must be sent to the investigators for acknowledgement and documented in the medical chart.
Source documents	Is it possible to download the forms from	No. This would not be acceptable according to Good Clinical Practice.

	the eCRF and use those as source documents?	
eCRF	Does the eCRF automatically send email notifications of pending queries?	No. Pending queries are not notified via email.

This project has received funding from the European Union's Horizon 2020 Research and Innovation programme under grant agreement No. 755094

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