INFORMATION SHEET AND INFORMED CONSENT FORM FOR THE PARENT(S) OR LEGAL GUARDIAN FOR THE ENROLLMENT OF A MINOR IN A CLINICAL TRIAL

Official title of the trial: Use of Mirtazapine in Rett syndrome: a phase II, multicentre, open-label, single-arm study.
Official title of the trial in more comprehensible terms for the patient: New use of the drug Mirtazapine in the treatment of patients with Rett syndrome, with typical disorders of the pathology.
Structure/context in which the trial will take place *To be completed by the clinical centre where the clinical trial will take place* *Name*_____ _____ |
Registry where the trial is or will be registered (if applicable) and any identifying code if available *To be completed by the clinical centre where the clinical trial will take place* Identifying code _____ Registry clinicaltrials.gov.....
Principal Investigator *(Indicate the Local Responsible for the trial)* *Name*_____ _____ | *Affiliation*_____ _____
EU CT Number 2024-515411-21-00
Sponsor/Funding body: University of Trieste, Department of Life Sciences (DSV) Via Giorgieri, n. 5 - Building Q - 34127 (Trieste)
Ethics Committee Pediatric Ethics Committee of the Tuscany Region

This document consists of the following sections:

A. PREAMBLE
B. INFORMATION SECTION. SUMMARY OF THE TRIAL: KEY INFORMATION
C. INFORMATION SECTION. FURTHER DETAILS
D. CONSENT SECTION
E. ATTACHMENTS
F. ADDITIONAL DOCUMENTS

Dear Madam/Sir, the information contained in the following information sheet is very detailed. We ask you to accept participation in the trial ONLY after having carefully read this information sheet and had a

THOROUGH CONVERSATION with a member of the trial team who must dedicate the NECESSARY TIME to you to fully understand what is being proposed to you.

A. PREAMBLE

Dear Madam/Sir (Guardian),

We propose the participation of your daughter/the patient in the clinical trial, which we illustrate below.

It is your right to be informed about the purpose and characteristics of the trial so that you can decide in a conscious and free manner whether to authorize participation.

This document aims to inform you about the nature of the trial, the purpose it proposes, what participation in it will entail, including your rights and responsibilities.

We invite you to carefully read the following. The researchers involved in this project, indicated at the beginning of this document, are available to answer your questions. No question that comes to mind is trivial: do not be afraid to ask it!

In addition to discussing with us, you can discuss the proposal contained in this document with your family doctor/paediatrician, your family members, and other people you trust. Take all the time you need to decide. You can take home an unsigned copy of this document to think about it or discuss it with others before making a decision.

If you decide not to allow your daughter/the patient to participate in the trial, your daughter/the patient will still receive the best possible care for patients with her condition/illness.

Your refusal will in no way be interpreted as a lack of trust.

Once you have read this form, had your questions answered, and possibly decided to authorize the participation of your daughter/the patient in the trial, you will be asked to sign a consent form, of which you will receive a paper copy.

The Principal Investigator

B. INFORMATION SECTION

GENERAL SUMMARY OF THE TRIAL: KEY INFORMATION

This section aims to briefly present the key aspects of the trial we are proposing for your daughter/the patient. The subsequent sections will provide more details to give you the opportunity to express or not a fully informed consent to the participation of your daughter in the trial.

- For what reason are we being asked to authorize participation in this trial?

We are asking for your consent to participate in a clinical trial funded by non-profit donations from Angelini SpA, Fondazione Amadei e Setti, Fondazione Canali and Fondazione Ico Falck because your daughter/the patient is affected by Rett Syndrome and we want to verify if the investigational therapy can lead to improvements in social behavior, respiratory area, and motor area. Your daughter/the patient has been included among those asked to participate in this trial because she presents some clinical characteristics that will be better specified in section C.

- What are the objectives of the trial? How many centers and patients will take part?

The trial is conducted to evaluate whether Mirtazapine can be used as a drug capable of inducing improvements in the patient with Rett syndrome, regarding her social behavior, respiratory capacity, and motor/physical condition. Other objectives of the trial are:

1. Evaluate the efficacy of MTZ in improving anxiety, depression, and mood.
2. Evaluate the efficacy of MTZ in improving sleep quality.
3. Evaluate the efficacy of MTZ in improving hand functionality.
4. Evaluate the improvement or worsening of the subject's overall clinical picture over time.
5. Evaluate the efficacy of the drug in improving the severity and number of symptoms associated with Rett syndrome.
6. Evaluate the efficacy of the drug in improving lung function.
7. Evaluate the improvement in parental/caregiver stress. The assessment scale used will be the Parenting Stress Index (PSI-SF).
8. Evaluate the improvement in levels of neurotrophic factors involved in the regulation of mood and cognition.

The trial is expected to take place in 4 Italian centers. The total number of participating patients is 54, aged between 5 and 40 years, divided into three groups of 18 patients each (5-10 years, 11-17 years, and 18-40 years).

- Is authorizing participation in the trial my free choice?

You can freely choose whether or not to authorize participation in the trial. Even after accepting, you can change your mind at any time.

- If I decide not to give consent to participate in the trial, what choices do I have?

If you decide not to allow participation in the trial, the patient can still be followed by the clinical center that cares for her and will be treated using the best approved (non-experimental) therapeutic methodologies for her disease.

Furthermore, she may participate in another possibly ongoing trial.

- What happens if I decide to authorize participation in the trial?

If participation in the trial is authorized, your daughter/the patient will be treated with the investigational drug for a maximum of 24 weeks. During the study and after each scheduled visit, she will be followed by doctors via telephone contact to assess the occurrence of any adverse events and to verify the tolerability of the administered dose of the investigational drug. Once the treatment is completed, she will be followed for a maximum of 4 weeks/1 month. The entire duration of her participation will be approximately 7 months.

To ensure therapeutic continuity, in patients with a rare disease and treated with clinical benefit within the "MirtaRett" clinical trial, we foresee recourse to "compassionate use" (according to Law No. 648/1996), which allows for the continued use of Mirtapil even after the conclusion of the clinical study.

Before taking part in the trial, the doctor will ask you to have some tests performed on your daughter/the patient and will verify if she has the required characteristics to participate.

The entire schedule of visits and tests planned during the trial is reported in the next section "What examinations, tests, and procedures are planned in the trial?"

- What are the risks and benefits if I authorize participation in the trial?

Participation in this trial may involve both risks and benefits. It is important to evaluate them carefully before making a decision.

- Expected benefits

By participating in the trial, we mainly expect that your daughter will have improvements in movement control, with benefits both in general movement and in specific difficulties such as muscle rigidity, feeding problems, and other motor disorders, including hand mobility.

Furthermore, the drug under investigation, mirtazapine, could improve sleep and reduce respiratory problems common in patients with Rett, such as irregular breathing and pauses in breathing, including apneas. Finally, we expect that the treatment could promote greater social interaction and reduce problematic behaviors such as irritability, aggression, and anxiety.

By adhering to the trial, you will contribute to the development of new drugs for Rett syndrome. In the future, other patients with the same pathology may also benefit.

- Potential risks

We want to be sure that you understand from the outset what some possible risks are: additional information can be found in the next section "*What risks might my daughter/the patient face if I authorize participation in this trial*?"

If you decide to allow your daughter/the patient to participate in this trial, it is not possible to predict all the side effects that may occur. Each person's reaction to an investigational drug can be different. The subject may experience a side effect or be at risk of unpredictable symptoms, diseases, and/or complications. The possible risks are reported in detail in the next section.

Your daughter/the patient will be carefully monitored for each of these reactions.

Two devices will be associated with the investigational drug:

- The *YouCare T-shirt,* a wearable device in the form of a shirt already on the market, which will allow cardiorespiratory monitoring and physical activity. It is widely used and validated in professional and amateur sports contexts and in the rehabilitation management of patients with neurological pathologies

and has recently been used successfully on 10 patients with Rett syndrome. No side effects and/or risks from its use have been reported;

- The *Motionlogger Micro Watch*, i.e., the wrist actigraph, a device that will allow monitoring of sleep quality. This is a widely validated and used device, therefore no side effects and/or risks from its use are reported.

- Is the consent final? Can I decide to withdraw my daughter/the patient from the clinical trial (voluntary withdrawal)?

You can decide to withdraw your daughter/the patient from the trial at any time and for any reason, without having to justify your decision.

If you decide to no longer have her participate in the trial, please inform one of the investigating physicians as soon as possible: it is important to suspend the treatment safely. The doctor might consider a final check-up visit/exam appropriate.

The doctor will keep you informed of any changes in the trial that may influence your willingness to continue authorizing participation.

- Are there reasons why the trial might be interrupted not by my will (early conclusion)?

Yes, the investigating physician may decide to interrupt the participation of your daughter/the patient in the trial if:

- Her health conditions should change and participation in the trial becomes potentially harmful;
- New information becomes available and the trial is no longer in her best interest;
- The agreed rules for participation in the trial are not followed, for any reason (such as difficulty in administering the drug to the patient);
- The trial is interrupted by the competent authorities or by the promoter.

You will be explained the reasons for the study interruption and you will be provided with advice to continue caring for the patient. It is essential that follow-up visits and scheduled treatments are respected, even if the study is interrupted due to withdrawal of consent, suspension of the trial, or other reasons.

C. INFORMATION SECTION. FURTHER DETAILS

1. What is the purpose of the trial?

This is a Phase II drug trial. The purpose of this trial is to evaluate the effect of mirtazapine, particularly in the treatment of some characteristics associated with Rett syndrome, such as sudden mood changes, motor symptoms (intensity and frequency of stereotypical hand movements), worsening sleep quality, behavioral aspects, and autonomic functionality. The study also aims to evaluate the overall efficacy of the study drug in patients with Rett syndrome, its safety, and tolerability. The efficacy of mirtazapine will be evaluated in relation to the age of the patient involved in the study (childhood, adolescence, and adulthood).

The dose of mirtazapine taken by each subject will depend on her age[.]{.underline} During the treatment period, the study drug (mirtazapine) will be taken orally, in the form of a solution (ml), once a day in the evening before bedtime. 54 patients with Rett Syndrome will participate in the trial, divided into 3 groups based on age, with 18 patients each:

- childhood (5-10 years);
- adolescence (11-17 years);
- adulthood (18-40 years).

From the day of the baseline visit (indicated as T0) to day 14 of the study, all involved patients will start with the minimum dose (Dose level 1) different for each age group. From the 15th day until Week 24 (180th day), the optimal dose will be reached, based on age, indicated as Dose level 2.

2. What is the intervention under investigation?

This study is single-arm, which means that all involved patients will receive the study drug, in the dosages and methods described in the previous paragraph.

If you give consent to participate in this study and if the study doctor confirms that the patient is eligible to take part, the study procedures will take place in the hospital where she normally receives medical care. The subsequent study follow-up will take place at the same hospital where the previous visits were conducted.

Patients can be included in the study only if all the following conditions are met:

1. Female, aged between 5 and 39 years.
2. Girls of childbearing age with a negative pregnancy test.
3. Body weight above 10 kg.
4. Diagnosis of Rett Syndrome confirmed by MECP2 gene mutation.
5. Respiratory problems (at least one of the following): periodic apnea, intermittent hyperventilation, breath holding, air swallowing, forced expulsion of air and/or saliva.
6. At least ten episodes per day of respiratory problems during wakefulness in the week preceding the screening visit (reported by the caregiver).
7. Stable drug regimen for 4 weeks before the start of the study.
8. Use of a highly effective contraceptive method, in patients of childbearing age.
9. Written consent signed by a parent, legal guardian, or representative before the screening visit.
10. Collaborative, willing, and able to complete the study with the assistance of the caregiver.
11. The caregiver is able to understand the study objectives and to collaborate.

Patients who meet one of the following exclusion criteria cannot be admitted to the study:

1. Is participating in another clinical trial in the experimental phase;
2. Hypersensitivity to mirtazapine;
3. Significant pathologies determined by the investigator, such as cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematological, or other problems, in addition to those related to RTT (such as severe diabetes mellitus, severe liver dysfunction, renal dysfunction, and other specific parameters);
4. Abnormalities in heart rhythm, detected by electrocardiogram (QTcF Interval on ECG > 450 msec);
5. Planned surgeries during the study;
6. Severe diabetes mellitus (hyperglycemia with values above the norm);
7. Pregnancy, breastfeeding;
8. Clinically significant malnutrition;
9. Patients who have manifested previous suicidal thoughts.

If your daughter/the patient is found to be eligible for participation in the study, the Drug that will be administered is mirtazapine - Mirtapil® in solution (ml) for oral use, to be taken once a day before going to sleep.

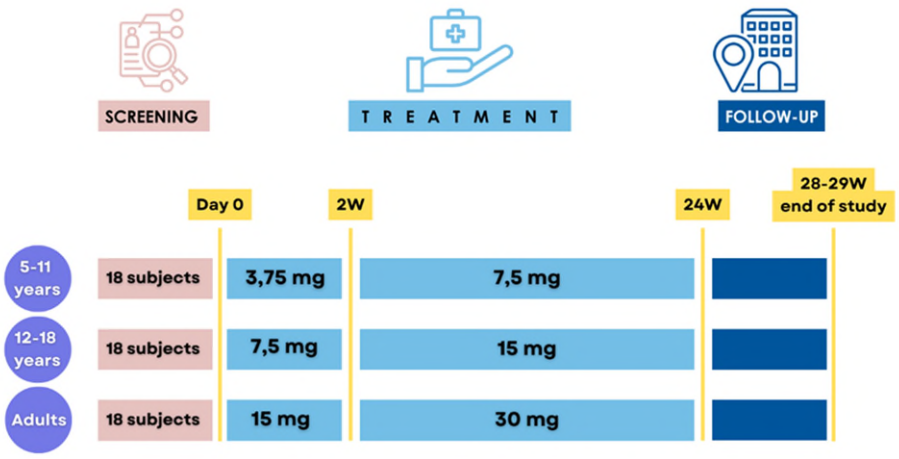
During the planned treatment period of 24 total weeks, the oral solution of the drug (dose level 1) will be administered based on age (3.75 mg for 5-10 years, 7.5 mg for 11-17 years, and 15 mg for > 18 years, days 1-14). From the 15th day to the 24th week, dose level 2 will be reached: 7.5 mg for 5-10 years, 15 mg for 11-17 years, and 30 mg for > 18 years.

Age groups	Dose level 1 (Day 1-14)	Dose level 2 (Day 15-180)
5 - 10 years	3.75 mg (0.25 ml)	7.5 mg (0.50 ml)
11 - 17 years	7.5 mg (0.50 ml)	15 mg (1 ml)
> 18 years	15 mg (1 ml)	30 mg (2 ml)

If there are no tolerability problems, patients will continue with the maximum tolerated dose (MTD) up to the final dose. If necessary, patients will receive a supply of study drug at the next visit. The date, time, and ml of solution administered by the healthcare operator will be recorded in a patient diary.

If intolerance develops at any time during the study, the investigator may reduce the patient's dose to a lower level, with a single dose interruption and administration on alternate days. Patients who are unable to tolerate the treatment even after a dose interruption must be suspended from the study.

Clinical trial scheme



3. What examinations, tests, and procedures are planned if I authorize participation in the trial?

The evaluation examinations planned for each visit are listed in the table below:

Type of Evaluation	**Screening** (up to 90 days before T0)	**T0** (Basal assessment)	**1St Phone contact** (2 weeks after T0)	**T1** (4 w ± 1 w from T0)	**2nd Phone contact** (8 w after T0)	**T2** (12 w ± 1 w from T0)	**3rd Phone contact** (16 w after T0)	**T3** (24 w ± 1 w after T0)	**Follow-up** (1 month after last dose of drug)
Informed consent	X								
Inclusion/Exclusion criteria	X	X							
Demografic data	X								
Medical Assessment	X								
Vital signs (body temperature, heart rate, respiratory rate and blood pressure)		X		X		X		X	X
ECG (12 derivations)		X		X		X		X	X
Physical examination including anthropometric assessment	X	X		X		X		X	X
Neurological examination	X	X		X		X		X	X
Blood sample collection (haematology, biochemistry and thyroid assessment)		X		X		X		X	
Collection of blood samples for metabolic biomarkers		X		X		X		X	

Type of Evaluation	**Screening** (up to 90 days before T0)	**T0** (Basal assessment)	**1St Phone contact** (2 weeks after T0)	**T1** (4 w ± 1 w from T0)	**2nd Phone contact** (8 w after T0)	**T2** (12 w ± 1 w from T0)	**3rd Phone contact** (16 w after T0)	**T3** (24 w ± 1 w after T0)	**Follow-up** (1 month after last dose of drug)
Serum prolactin		X		X		X		X	
Serum ACTH and cortisol		X		X		X		X	
Serum pregnancy test (for post-pubertal patients)	X	X		X		X		X	
Blood sample for neuronal plasticity (BDNF, GDNF, PDGF)		X				X		X	
Polysomnography test (only in Genoa and Milan)		X						X	
Actigraphy using a wrist sensor		X				X		X	
Cardiorespiratory and condition monitoring at home (YouCare T-shirt, 24 hours)		X		X		X		X	
Severity assessment scale (RCSS)		X		X		X		X	
Behavioral and motor assessment scale (MBAS)		X		X		X		X	
Mood assessment ascale (ADAMS)		X		X		X		X	
Rett Syndrome Behaviour Questionnaire (RSBQ)		X		X		X		X	
Purposeful Hand Function rating Scale (PHF)		X		X		X		X	
Sleep Disturbancies Scale for Chlldren (SDSC)		X		X		X		X	
Global Clinical Impression of Change (CGI-C)		X		X		X		X	X
Parenting Stress Index (PSI-SF)		X				X		X	
Treatment		X	X	X		X			
Compliance with treatment in the study (review of patient diary)			X	X	X	X	X	X	
Return of treatment kits and YouCare T-shirt								X	
AE Review		X	X	X	X	X	X	X	X
SAE Review		X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X

During the study, in-depth diagnostic investigations on blood samples (such as those related to neuronal plasticity) to which the patient will be subjected may reveal additional and/or unexpected information, i.e., data that were not initially sought, but which could have an impact on the patient's health and be useful for her treatment or for making important decisions regarding it. This information will be communicated to you only upon your request

4. What risks might my daughter/the patient face if I authorize participation in the trial?

It is not possible to predict all the side effects of a treatment. Each person can react differently to an investigational drug and the patient might experience unforeseen side effects.

Below are the possible inconveniences and risks related to the participation of your daughter/the patient in this study. Possible risks may be related to the main side effects due to the use of mirtazapine or to procedures planned by the study, such as discomfort related to blood draws.

The main known side effects related to the use of mirtazapine are:

Very common (more than 1 in 10 people)	*•increased appetite and weight gain* *•drowsiness or lethargy* *•headache* *•dry mouth*
Communes (may affect up to 1 in 10 people)	*•lethargy* *•dizziness* *•agitation or tremors* *•nausea* *•diarrhoea* *•vomiting* *•difficult, incomplete or infrequent bowel movements (constipation)* *•rash or skin eruptions (exanthema)* *•joint pain (arthralgia) or muscle pain (myalgia).* *•back pain* *•feeling dizzy or faint when standing up quickly (orthostatic hypotension)* *•swelling (usually of the ankles or feet) due to water retention (oedema)* *•tiredness* *•realistic dreams* *•confusion* *•feeling anxious* *• sleeping troubles*
Uncommon (may affect up to 1 in 100 people)	*•feeling of euphoria or extreme well-being (mania)* *•abnormal skin sensations, such as burning, stinging, tickling or tingling (paresthesia)* *•restless legs syndrome* *•loss of consciousness (syncope)* *•numbness in the mouth (oral hypoesthesia)* *•lowering of blood pressure.* *•nightmares* *•feeling of agitation* *•hallucinations* *•strong urge to move*
Rare (may affect up to 1 in 1,000 people)	*•yellowing of the eyes or skin, which may indicate liver dysfunction (jaundice)* *•muscle spasms or twitching (myoclonus)*

	•aggression *•severe stomach pain that may spread to the back. This may be a sign of pancreatitis*
Not known (frequency cannot be determined based on available data)	*•Signs of infection such as unexplained high fever, sore throat and mouth ulcers (agranulocytosis).* *•In rare cases, Mirtazapine EG can cause disturbances in blood cell production (bone marrow depression).* *•Some people become less resistant to infections as Mirtazapine EG can cause a temporary deficiency of white blood cells (granulocytopenia). In rare cases, Mirtazapine EG can also cause a deficiency of red and white blood cells as well as platelets (aplastic anaemia), a deficiency of platelets (thrombocytopenia) or an increase in the number of white blood cells (eosinophilia).* *•Severe skin reactions (Stevens-Johnson syndrome, bullous dermatitis, erythema multiforme, toxic epidermal necrolysis).* *•Epileptic seizure (convulsions)* *•A combination of symptoms such as unexplained fever, sweating, increased heart rate, diarrhoea, muscle contractions (uncontrollable), chills, overactive reflexes, agitation, mood changes and unconsciousness. In very rare cases, these may be signs of serotonin syndrome.* *•Self-harming or suicidal thoughts* *•Abnormal sensations in the mouth (oral paraesthesia)* *•Swelling of the mouth (oral oedema)* *•Increased salivation* *•Difficulty speaking (dysarthria)* *•Sleepwalking (somnambulism)* *•Hyponatraemia* *•Syndrome of inappropriate antidiuretic hormone secretion.* *•Increased blood creatine kinase levels* *•Difficulty urinating* *•Muscle stiffness and/or weakness and darkening and discolouration of urine (rhabdomyolysis)*

In case of questions regarding the possible risks listed above, you can contact the doctors involved in the study. It is important to inform the responsible study doctor of any change in the health status of your daughter/the patient as soon as it occurs, regardless of whether you believe it was caused by the study drug. If a medical problem arises as a consequence of the study, your daughter/the patient will still be ensured the most suitable care.

5. How will I be informed of any unexpected results following diagnostic investigations?

During the study, unexpected results may emerge. The study doctor will provide you with such information only if you accept to be informed.

6. Is it useful/necessary to inform my family doctor/paediatrician?

If you decide to authorize the participation of your daughter/the patient in this trial, it is important that you inform your general practitioner/paediatrician. For this purpose, we have prepared a letter that you can give to him/her, which illustrates the procedures of the trial.

7. What will be the commitment of my daughter/the patient and what are the responsibilities if I decide to authorize her participation?

If you decide to authorize your daughter/the patient to participate in this trial, you will be required to:

- *Provide written consent for your daughter's participation in this research study;*
- *Provide an authorization form for the use, disclosure, and transfer of your daughter's personal health data (refer to the Privacy Policy);*
- *Scrupulously observe the instructions and requests from the healthcare personnel following the trial and ensure attendance at appointments.*
- *Inform the doctor following the trial:*
  - of all medications your daughter/the patient is taking including non-conventional drugs,
  - of any side effect that arises during the trial,
  - of any visit or hospital admission in facilities other than the investigating center,
  - of current or previous participation in other clinical trials.

- Record in the diary every time the investigational drug is taken at home.
- Avoid pregnancy or breastfeeding during the trial.
- Answer questions from the study doctor or study team after your daughter/the patient has been taken home;
- Report any medical problems or side effects encountered in the patient during participation in the study.

8. Will I have to face costs for participation in the trial? Will I be reimbursed for any expenses? Will my daughter/the patient receive compensation?

All treatments and examinations related to the study are free of cost. These costs will be covered by the company sponsoring this study. The patient's participation in the study does not involve any additional cost. No financial compensation is provided for participation in the trial.

9. What happens if my daughter/the patient suffers harm as a consequence of participation in the trial?

Participation in a clinical trial may involve inconveniences and risks not determinable a priori. For this reason, the clinical trial provides insurance coverage to protect the participation of your daughter/the patient.

In compliance with current laws, insurance is arranged to cover any damages suffered due to participation in the trial, for the entire period of the same, covering the civil liability of the investigator and the promoter.

The insurance, details of which can be obtained upon request, is as follows:

> Insurance company: HDI-GLOBAL SE
> Policy number: 390-01586937-30018
> Maximum per patient: € 1,000,000.00
> Maximum per protocol: € 7,500,000.00

It should be specified that, according to the Ministerial Decree of July 14, 2009, the insurance policy does not cover the value exceeding the maximum limit and is operative exclusively for damages whose claim for compensation has been submitted no later than the period foreseen in the policy (120 months from the end of the Trial). This limitation does not, however, affect the right to obtain compensation from the responsible party for any damage (to protect the trial subject).

10. How will my daughter's/the patient's health data, including identifying data, be treated and who will have access to it during the trial?

Only the personal data necessary for the purposes of the study will be recorded in the electronic storage system of the study. Your written consent is required for the use of this information in the study by signing this form.

Your daughter's/the patient's data, in particular demographic and health data, will be processed only to the extent that they are essential for the objective of the trial and for pharmacovigilance purposes, in compliance with EU Regulation 2016/679, known as GDPR (General Data Protection Regulation) and Legislative Decree No. 101 of August 10, 2018.

The study doctor will collect the data according to the study protocol approved by the competent authorities. The identity of your daughter/the patient will be known only to the study staff, legally bound by professional secrecy. All data and samples collected within the study will be processed in a coded format, meaning all individual identifiers (identity code, name, etc.) will be replaced by code numbers and the data or samples cannot be directly identified in the study results, reports, or publications related to the study itself. These identifiers will be stored separately from the coded data. The study doctor will continue to know your daughter's/the patient's name, identity code, and contact details without these being communicated to the Study Promoter.

The anonymized data may be submitted for review by regulatory bodies and used for scientific publications (journals, conferences). The patient's clinical data collected for the purposes of the trial, as well as the results of the tests performed, will be stored for the time required by regulations and subsequently destroyed. They will not be destroyed only if a) it is no longer possible to trace the identity of your daughter/the patient, because they were anonymized during the trial itself; b) in the presence of your specific informed consent.

There are some circumstances in which the personal data and medical records of you and your daughter/the patient may be shared, without revealing your identity and that of your daughter/the patient, with people and organizations conducting or monitoring this study, including:

- People who collaborate with or represent the Promoter;

• Government agencies, such as EMA, for inspections;
• People who monitor and evaluate data in contract research organizations and in the data safety monitoring board that ensure the proper conduct of the study;
• The Ethics Committees that have reviewed this study;

Your daughter's/the patient's study doctor, the study team, the hospital, the Promoter, and its representatives are required by law to keep your daughter's/the patient's medical data and coded data confidential, with some exceptions allowed by law or by EMA for inspection purposes.

We reserve the right to publish the results and data of this research. However, your daughter's/the patient's name and personal identifiers will never be disclosed.

If you decide to interrupt your daughter's/the patient's participation in the study or if the cause of the interruption is related to the study doctor, the data collected before the interruption will be used as part of the study data. This is essential to ensure the reliability of the study results and the safety of the study subjects. The Promoter will not collect other personal data of your daughter/the patient after you have withdrawn her from the study.

Further information is contained in the Privacy Policy that you will receive.

11. How will the biological samples of my daughter/the patient taken for the purposes of the trial be treated and who will have access to them?

As with health data, biological samples will also be used for the purposes of the trial in a pseudonymized manner (a technique that allows modifying and masking the personal and sensitive data of an individual, in order not to make them directly and easily attributable to her), meaning they contain exclusively the subject's identification number[,]{.underline} specific to the study[,]{.underline} of your daughter/the patient.

Your daughter's/the patient's blood samples will be used exclusively for this study. The samples will be analyzed in the local hospital's laboratory and in the research laboratory of the University of Trieste, Sponsor of this study.

Once the trial is over, the samples will be destroyed.

12. How can I have access to the results of the trial?

Once the trial is concluded and all resulting data are collected, they will be analyzed to draw conclusions. The investigators commit to making them available to the scientific community.

The law provides the possibility for participants to have access to the trial results. Therefore, you can ask the investigating physician to report the general results of the trial to you.

It is your right to view the personal data of your daughter/the patient collected and to request any corrections. Upon your request, you will also be informed from where the data were collected and where/to whom the data and/or samples have been disclosed/transferred. Please note that it is often possible to view the collected data only after the conclusion of the study.

You can receive the data free of charge in a structured, common computer format (readable electronic text or graphic file). Furthermore, you have the right to request the deletion of personal data if you decide to

withdraw consent or interrupt the patient's participation in the study. You also have the right to file a complaint with a data protection authority in Italy.

Contact details:
Piazza Venezia 11 -- 00187 Rome (Italy)
Phone: + 39 06.696771
E-mail address: protocollo@gpdp.it

If the study doctor has included your daughter/the patient in the study, you have the right to object to the use of her data collected up to that moment for the study. In that case, we invite you to inform the study doctor.

A description of this study will be available on the EU Clinical Trials Register https://euclinicaltrials.eu/, as required by EU Regulation. This website will not include information capable of identifying the patient. Upon study completion, the website will contain at most a summary of the study results. You can search this website at any time.

13. Has the trial been approved by the Ethics Committee?

The protocol of the trial proposed to you has been reviewed and approved by the Pediatric Ethics Committee of the Tuscany Region on **13th February 2025**. The Ethics Committee has, among other things, verified the conformity of the trial to the EU Good Clinical Practice Standards and the ethical principles expressed in the Declaration of Helsinki and that the safety, rights, and well-being of your daughter/the patient have been protected.

14. Who can I refer to for more information about the clinical trial to which my daughter/the patient has been invited to participate?

If you have questions about your rights or have reports regarding the processing of your personal data or that of your daughter/the patient, you can contact the specific contact point for this trial or the data protection officer of the Promoter. You can contact them at the following numbers:

name: Pediatric Ethics Committee of the Tuscany Region
phone: 055 5662386
E-mail: comitato.etico@meyer.it
address: Viale Pieraccini 24, 50139 Florence

(Note: We invite you to provide the name of the data protection officer DPO of the Promoter, together with the address and contacts)

name: Valentina Carollo, Legant S.T.A.R.L. - Rovereto (TN) Italy
E-mail: [[dpo@units.it]{.underline}](mailto:dpo@units.it)
address: University of Trieste -- Piazzale Europa 1 -- 34100 Trieste

15. In case I decide to authorize adherence to the trial, who can I contact if necessary?

If you have questions, doubts, complaints, or believe that this study has caused harm to your daughter/the patient or caused her illness, you can contact the study doctor or a member of the study staff, using the telephone numbers listed below:

(Note: We invite you to provide the name of the study doctor/principal investigator or member of the study staff of the center/hospital, together with the address and telephone number).

name: _____ telephone: (_____)
_____

E-mail:
_____

address:
_____

name: _____ telephone: (_____)
_____

E-mail:
_____

address:
_____

If there is a need to call after working hours or on weekends, we invite you to use the numbers listed below:

name: _____ telephone: (_____)
_____

E-mail:
_____

address:
_____

name: _____ telephone: (_____)
_____

E-mail:
_____

address:
_____

If you deem it appropriate to report events or facts related to the trial to which your daughter/the patient has adhered to subjects not directly involved in the trial itself, you can contact the Ethics Committee that approved the trial (Pediatric Ethics Committee of the Tuscany Region), the Health Directorate of the Trial Center, the competent authority (AIFA).

Attachments

- Insurance policy
- Form for consent to data processing

Additional documents:

- Letter for the doctor/paediatrician

D. CONSENT SECTION FOR THE PARENT(S) OR LEGAL GUARDIAN OF THE PATIENT

(Notes: 1 copy for the participant, 1 copy for the trial responsible)

Patient's name _____

Place and date of birth of the patient _____

Title of the trial: Use of Mirtazapine in Rett syndrome: a phase II, multicentre, open-label, single-arm study

Protocol Code, version and date: MirtaRett, 1.0 of July 16, 2024

Trial promoter/sponsor/funding body: University of Trieste, Department of Life Sciences (DSV), Via Edoardo Weiss 2 - 34128 (Trieste)

Principal Investigator

Name _____

Affiliation _____

Contacts (mail) _____(***Phone***)_____

I, the undersigned _____

born in _____ on ___/___/_____

as mother/legal guardian of the patient mentioned above;

I, the undersigned _____

born in _____ on ___/___/_____

as father/legal guardian of the patient mentioned above;

DECLARE/DECLARE

☐ that we have received from Dr. _____ comprehensive explanations regarding the request to participate in the research in question, as reported in the information section, which is part of this consent form, a copy of which was given to us on _____ at _____ (indicate date and time of delivery);

☐ that the nature, purpose, procedures, expected benefits, possible risks and drawbacks, and alternative treatment options to the proposed clinical trial have been clearly explained to us/me and we/I understand them;

☐ that we/I have had the opportunity to ask the study investigator any questions and have received satisfactory answers;

☐ that we/I have had sufficient time to reflect on the information received;

☐ that we/I have had sufficient time to discuss it with third parties;

☐ that we/I have been informed that the trial protocol and all the forms used have been approved by the relevant Ethics Committee;

☐ that we/I are aware that the research may be interrupted at any time, at the discretion of the research manager;

☐ that we have been informed that we will be made aware of any new data that may compromise the safety of the research and that, for any problems or further questions, we can contact the doctors treating our/my daughter/the minor;

☐ that for the best protection of our/my daughter's/the patient's health, we are aware of the importance (and our/my responsibility) of informing the general practitioner/paediatrician of our choice about the trial in which we agree to allow our daughter/the patient to participate. We are aware of the importance of providing all information (medications, side effects, etc.) concerning our/my daughter/the patient to the investigator;

☐ that we have been informed that the results of the trial will be disclosed to the scientific community, protecting the identity of our/my daughter/the patient in accordance with current privacy legislation;

☐ that we are aware that any choice expressed in this consent form may be revoked at any time and without justification;

☐ that we consent to the completion of the questionnaires required by the study;

☐ that we have received a copy of this consent form.

WE/I therefore DECLARE that

☐ we/I want ☐ we/I do NOT want our/my daughter/the patient to participate in the trial

☐ want ☐ NOT want to be informed of any unexpected news relating to the present or future health of our/my daughter/the patient, which may incidentally emerge from the investigations required by the trial, when this may involve possible benefits

_____ ___/___/_____ _____ _____

Mother's full name Date Time Signature

_____ ___/___/_____ _____ _____

Father's full name Date Time Signature

_____ ___/___/_____ _____ _____

Full name of legal representative Date Time Signature