Clinical Trial Summary

Efficacy and safety of 2 doses of agomelatine (10mg, 25mg) given orally in children (from 7 to less than 12 years) and adolescents (from 12 to less than 18 years) with moderate to severe Major Depressive Disorder.

Full scientific title: Efficacy and safety of 2 doses of agomelatine (10 mg, 25 mg) given orally in children (from 7 to less than 12 years) and adolescents (from 12 to less than 18 years) with moderate to severe Major Depressive Disorder. A 12-week, randomized, double-blind, active (fluoxetine 10 mg/day with potential adjustment to 20 mg/day) and placebo-controlled, parallel groups, international, multicentre study followed by an optional open-labelled 21-month safety extension period.

We thank all the participants who took part in the study. Clinical study participants are very important for making progress in science, for the benefit of patients.
This document is a summary of the study. It is written for a general audience.

Researchers need many studies to decide which medicines work the best and are the safest for patients. For medical science to progress, many studies involving patients are running all around the world. This summary only shows the results from this one study. Other studies, evaluating the same drug, may find different results. You should not change your current treatment based on the results of this single study. If you have any questions about this study, please talk to your doctor.

Therapeutic area:
Psychiatry

Disease:
Major Depressive Disorder

Study phase:
Phase 3

21st April 2022

Final version

In this summary:

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1 Why was this study done?

The study was done to test if a drug called agomelatine can help children and adolescents with depression.

Agomelatine is already used in adults with depression. Researchers expected that it could be useful for children and adolescents as well.

Depression has a variety of symptoms. Symptoms may include feelings of sadness, changes in appetite, concentration or sleep…and so on.

This study is called a Phase 3 study.

The main goal of the study was to test if agomelatine works better than placebo* for depression in children and adolescents after 3 months of treatment.

*A placebo looks like a medicine but does not contain any real medicine.

2 When and where did this study take place?

When did the study take place?

- This study started in February 2016.
- It ended in October 2021.

A first clinical trial summary was done in October 2020 while the study was still on-going. It is available on the Servier Clinical Trial website (1st summary in 2020).

The first summary included information collected during the first part of the study. The current summary includes information collected during the whole study.

Where did the study take place?

The study took place in the following countries:

Country	Number of participants
Russia	120
Hungary	74
Ukraine	72
Romania	61
Poland	31
South Africa	17
Serbia	10
Bulgaria	9
Finland	6

3 Who participated in the study?

Which participants were included in the study?

To take part, participants had to:

- Be aged from 7 to 11 years old (child) or from 12 to 17 years old (adolescent).
- Have moderate or severe depression.
- Not have high risk of suicide.
- Not have high risk of liver disorder.

How many participants took part in the study?

A total of 400 participants took part in the study: 320 were adolescents and 80 were children. About 2 out of 3 participants were girls.

How old were the participants at the beginning of the study?

The average age of the children was 9 years old. The youngest child was 7 years old and the oldest one was 11 years old.

The average age of the adolescents was 15 years old. The youngest adolescent was 12 years old and the oldest was 17 years old.

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4 Which treatments did the participants receive?

During the first part of the study, the participants received either:

- the study medicine, or
- a reference medicine already authorised to treat children and adolescents with depression, or
- a placebo that did not contain the real medicines.

The study medicine was called agomelatine. It was a tablet of 10 or 25 mg of active medicine. Participants took the tablet orally in the evening at bedtime.

The reference medicine was fluoxetine, first given in a dose of 10 mg, with a possible increase to 20 mg. Fluoxetine is the only medicine currently authorised and available for children and adolescents with symptoms of depression. This treatment was included in the study as a control, already known to be effective.
It was given as an oral solution of:

- 2.5 ml (half a teaspoon, containing 10 mg of active medicine), or
- 5 ml (one teaspoon, containing 20 mg of active medicine).

Participants took fluoxetine in the morning upon awakening.

Both agomelatine and fluoxetine were compared to placebo.

The placebo looked like agomelatine (tablet) and fluoxetine (solution) but did not contain the real medicines.

During the second part of the study, all the participants who wanted to continue the study, were given agomelatine. It was a tablet of 10 or 25 mg of active medicine.

5 How was the study carried out?

The study was split into 2 main periods.

- First part of the study

The study was called a “randomized” study. This means that participants were put by chance into one of the 4 following groups:

- 102 participants took 10 mg of agomelatine.
- 95 participants took 25 mg of agomelatine.
- 103 participants took placebo.
- 100 participants took fluoxetine (10 mg possibly increased to 20 mg).

The study was also called a “double-blind” study. This means that neither the participants, nor their parents, nor the research doctors knew which treatment was taken. This was to avoid any influence on the results.

Each participant took both:

- the oral solution (placebo or fluoxetine) in the morning and
- a tablet (placebo or agomelatine) in the evening.

After 2 weeks, if the doctor found that there was no improvement, the dose of oral solution (placebo or fluoxetine) was increased from half a teaspoon to one teaspoon.

The first part of the study ended after 3 months of treatment.

- Second part of the study

After that, all participants could continue the treatment with agomelatine alone up to 2 years. This was the second part of the study: 339 patients took part.

This part was called “open-label”. This means that the participants, the parents and the research doctors knew that only agomelatine was taken.

This part was done to assess how safe and efficient agomelatine was when used for a long time (around 2 years).

During the whole study, the child or adolescent met the doctors regularly to talk about his/her depression symptoms.

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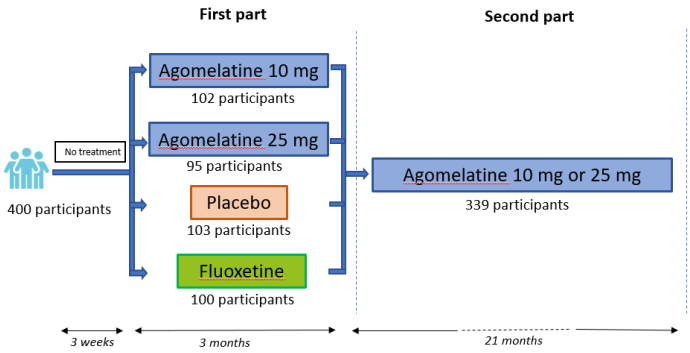
The study design is presented in the image below.



6 What were the side effects?

Side effects are unwanted medical events that the doctors think may be caused by the treatments in the study.
Side effects that occurred during the first part of the study are presented in the 1st summary in 2020 available on the Servier Clinical Trials website.

In this summary, we describe unwanted medical events thought to be caused by agomelatine.
The results may be presented differently in other documents related to the study.

The table below shows the number of participants who had side effects during the second part of the study and during the whole study.

	Second part of the study	Whole study
	Out of the 339 participants treated with agomelatine	Out of the 170 participants** treated with agomelatine from the beginning
Participants who had side effect(s)	49 (14.5%)	63 (37.1%)
Participants who had serious* side effect(s)	0	0
Participants who stopped the treatment because of side effect(s)	3 (0.9%)	1 (0.6%)

**See definition of serious side effects below*
***170 participants in the second part*

What were the side effects?

The table below shows the most common side effects reported in the study (reported by more than 3 participants).

	Second part of the study	Whole study
	Out of the 339 participants treated with agomelatine	Out of the 170 participants* treated with agomelatine from the beginning
Headache	8 (2.4%)	8 (4.7%)
Dizziness	7 (2.1%)	7 (4.1%)
Dry mouth	6 (1.8%)	27 (15.9%)
Thirst	6 (1.8%)	20 (11.8%)
Sleepiness	4 (1.2%)	3 (1.8%)
Increase in liver enzyme called ALT	4 (1.2%)	3 (1.8%)
Feeling sick	3 (0.9%)	15 (8.8%)
Stomach pain	1 (0.3%)	5 (2.9%)
Increased appetite	1 (0.3%)	4 (2.4%)

= participants
**170 participants in the second part*

What were the serious side effects?

A side effect is considered serious when:

- the participant needs to be hospitalised,
- it causes lasting damage or death,
- the participant's life is in danger or,
- it is medically important in the doctor's opinion.

No participant reported a serious side effect during the second part of the study.

The 3 participants who had serious side effects during the first part of the study stopped their treatment. These participants did not join the second part of the study. Their side effects are described in the 1st summary in 2020.

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7 What were the study results?

The study was completed as planned.

The doctors assessed the symptoms of depression with the participants and with their parents at each visit. For that, doctors used a questionnaire called CDRS-R (Children's Depression Rating Scale Revised). At each visit, doctors obtained a score on the CDRS-R.

After 3 months of treatment, CDRS scores improved. This means that over 3 months of treatment participants who took agomelatine 25 mg were less depressed, on average, than participants who took the placebo. Results are more detailed in the 1st summary in 2020.

During the second part of the study, the CDRS score was still improving, over the 21-months of treatment with agomelatine. This means that participants were still improving regarding the depression.

This document presents only the results for the main goal of the study. Other results are available in other documents listed in section 10.

8 How has this study helped research?

The study found that participants who took agomelatine 25 mg were less depressed, on average, than participants who took the placebo. Similar results were found in the adolescent' group (12-17 years old). There were too few children (7-11 years old) in the study to know if agomelatine works for them on depression.

Throughout the 2-year study, patients continuously improved with agomelatine.
Moreover, the study found that the side effects in adolescents who took agomelatine were similar to those known in adults.

This summary shows only the results from this one study. Other studies, evaluating the same drug, may find different results.

9 Are there plans for further studies?

No other study with agomelatine is planned so far.

10 Further information

What are the identification numbers of the study?

- Protocol code: CL3-20098-076
- EudraCT number: 2015-002181-23

Who did the study?

The company that organised and funded the research, called the "sponsor", is the Institut de Recherches Internationales Servier based in Suresnes, France.

How can you contact the sponsor?

Contact us on the Servier website https://servier.com/en/.

Where can you learn more about this study?

You can find more information about this study on these websites:

- https://clinicaltrials.servier.com/find/-clinical-trial
- https://www.clinicaltrialsregister.eu/ctr-search

In this document we translated medical terms into lay terms. You can find the corresponding medical terms in the Servier glossary at https://clinicaltrials.servier.com/glossary/
You can find general information about clinical trials on https://clinicaltrials.servier.com/