Clinical trial SUMMARY

Short study title

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.

In this summary:

Therapeutic area:
Psychiatry

Indication:
Major Depressive Disorder

Study phase:
Phase 3

20 October 2020
Final version

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.

We would like to thank all children, adolescents and their parents who participated in the study. Thanks to their involvement in this clinical study, they are helping researchers discover new drugs for the benefit of all patients.
This document is a summary of the study. It is written for a general audience.

Researchers need many studies to decide which medicines are the safest and the most effective for patients. For medical science to progress, a lot of people are involved in many studies 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 or your parents should not change your current treatment based on the results of this single study. If you or your parents have any questions about this study, please speak to your doctor.

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…

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.
A placebo looks like a medicine but does not have any real medicine in it.

2 When and where did this study take place?

When was it performed?

- This study started in February 2016.
- The first part of the study ended in January 2020.

The second part of the study is still on-going.

This summary only includes information collected for the first part of the study.

Where did the study take place?

The study took place in the following countries:

Country	Number of patients
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 patients were included in the study?

To take part, patients had to meet specific criteria, including:

- Be aged from 7 to 11 years old (child) or from 12 to 17 years old (adolescent).
- Have moderate or severe depression.
- Have no high risk of suicide.
- Have no high risk of liver disorder.

How many patients participated in the study?

Overall, 400 patients joined the study: 320 were adolescents and 80 were children. About 2 patients out of 3 were girls. 48 patients did not complete the treatment planned in the study mainly due to non-medical reasons.

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How old were the patients?

The average age of the children was 9 years. 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.

4 Which treatments did patients receive?

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

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

The study medicine was called agomelatine. It was a tablet of 10 or 25 mg of active medicine. Patients 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 in pharmacy 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).

Patients 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.

5 How was the study done?

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

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

Among the 400 patients enrolled, one patient stopped the study before receiving the treatment.

The study is also called a “double-blind” study. It means that neither patients, nor their parents, nor doctors knew who was given which treatment. Therefore, there was no influence of patients and doctors on study results.

Each patient took:

- 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.

During the study, the child or adolescent met the doctors regularly to talk about their depression symptoms.

The first part of the study ended after 3 months of treatment.
After that, patients could continue the treatment with agomelatine alone up to 2 years. This is the second part of the study which is still on-going.

This summary describes only the results of the first part of the study.

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6 What were the side effects?

What about side effects?

Like all medicines, the study drug can cause side effects, although not everybody gets them. Side effects are unwanted events thought to be related to the treatments in the study.

The table below shows the number of patients who experienced side effects on treatment.

	Related to 10 mg agomelatine	Related to 25 mg agomelatine	Related to Placebo	Related to fluoxetine
Patients who had side effect(s)	30 patients (29.4%)	35 patients (37.2%)	28 patients (27.2 %)	29 patients (29 %)
Patients who had serious* side effect(s)	0	1 patient (1.1%)	0	2 patients (2.0%)
Patients who withdrew because of side effect(s)	0	3 patients (3.2%)	1 patient (1.0%)	3 patients (3.0%)

**See definition in the section below*

How many patients had serious side effects?

A side effect is serious when:

- the patient needs to be hospitalized,
- the patient's life is in danger,
- it causes permanent damage or death,
- or it may put the patient at risk and requires a medical intervention to prevent the situations listed above.

In this study, 3 patients had serious side effects:
With agomelatine 25 mg:

- One patient had poor activity of a gland called the thyroid.

With fluoxetine:

- One patient had increased liver enzyme called ALT and AST.
- One patient had suicidal thoughts.

As a consequence of the serious side-effects, treatment was terminated for these 3 patients.

What were the other side effects?

The table below shows the other side effects reported in the study. Only the most common (reported by at least 3 patients in one of the agomelatine groups) are presented. Be aware that results may be presented differently elsewhere.

	Related to 10 mg agomelatine	Related to 25 mg agomelatine	Related to placebo	Related to fluoxetine
Dry mouth	17 patients (16.7%)	12 patients (12.8%)	9 patients (8.7%)	10 patients (10%)
Thirst	12 patients (11.8%)	9 patients (9.6%)	8 patients (7.8%)	10 patients (10%)
Feeling sick	6 patients (5.9%)	9 patients (9.6%)	8 patients (7.8%)	5 patients (5%)
Stomach pain	2 patients (2%)	3 patients (3.2%)	1 patient (1%)	1 patient (1%)
Headache	4 patients (3.9%)	2 patients (2.1%)	3 patients (2.9%)	5 patients (5%)
Dizziness	3 patients (2.9%)	2 patients (2.1%)	2 patients (1.9%)	2 patients (2%)

In addition, increased appetite and weight gain were reported more frequently in the agomelatine group than in the placebo group. These events were rarely thought to be related to the study treatments.

7 What were the study results?

The first part of the study was completed as planned.

The doctors assessed the symptoms of depression with the patients 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. The lower the score, the less depression there was.

In all groups, the CDRS score decreased from the beginning to the end of the treatment. This means that depression improved in all groups of treatments.

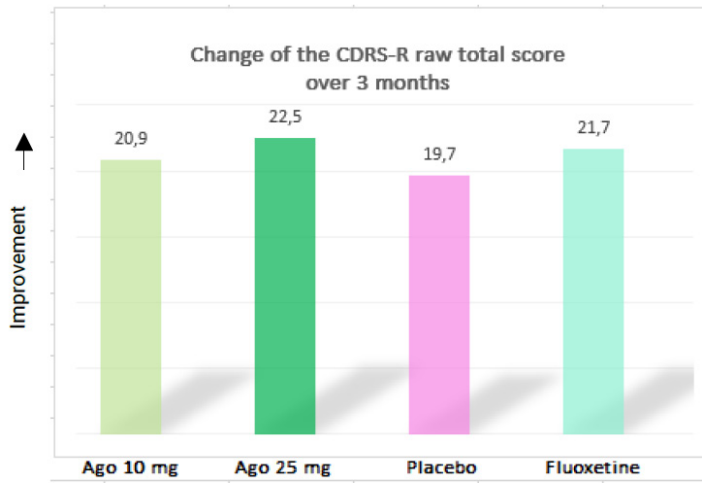
After 3 months of treatment, the CDRS score was lower with agomelatine and fluoxetine than with placebo.

The difference in depression scores between the agomelatine 10 mg and the placebo groups was not large enough. This means that with agomelatine 10 mg, the improvement of depression is likely to be the result of chance rather than caused by the treatment.

The difference between the agomelatine 25 mg and the placebo groups was significant in the overall population of the study.
This means that patients who took agomelatine 25 mg were less depressed, on average, than patients who took the placebo.

The study also confirmed that fluoxetine works on depression.

The chart below shows how much the CDRS scores decreased in all patients over 3 months of treatment. The higher the bar in the graph is, the more the depression improved.



Similar results were found in the adolescent group with agomelatine 25 mg.
There were too few children in the study to know if agomelatine works for them on depression.

8 How has this study helped patients and researchers?

This study helped researchers and doctors gather more information on depression for children and adolescents.

9 Are there plans for further studies?

No other studies to evaluate the short-term efficacy and safety of agomelatine in children and adolescents with depression are foreseen to date.

10 Further information

What is the identification number of the clinical study?

- Protocol Number: CL3-20098-076
- EudraCT Number: 2015-002181-23

Who did the study?

The company organizing and funding 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 (www.servier.com).

Where can you learn more about this study?

- The scientific study summary is also available on the Servier Clinical Trial Data website. (www.clinicaltrials.servier.com)
- In this document we translated medical terms into lay terms. You can find the corresponding medical terms in the Servier glossary on the Servier Clinical Trial Data website.