Plain Language Summary of Publication: A comparison of once-monthly and once-every-2-months injectable formulations of aripiprazole in people with schizophrenia

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Leslie Citrome[1], Pedro Such[2], Murat Yildirim[2], Jessica Madera-McDonough[3], Clodagh Beckham[4], Na Jin[3], Suzanne Watkin[3], Zhen Zhang[3], Frank Larsen[2] and Matthew Harlin[3]

Summary

The purpose of this summary is to explain key findings from a study that included people with schizophrenia, as described in two separate articles (see the 'Further Information' section for more details).

The study compared a new formulation of aripiprazole, given as an injection once every 2 months, with a once-monthly injection of aripiprazole.

How to say...

How to say the medical terms used in this summary

- **Abilify Asimtufii**: <a-BIL-i-fy a-SIM-tuh-FYE>
- **Akathisia:** <ack-uh-thizh-uh>
- **Antipsychotic:** <an-tie-sy-COT-ick>
- **Aripiprazole:** <a-ri-PIP-ruh-zol>
- **Pharmacokinetic:** <faar-muh-ko-kuh-neh-tik>
- **Schizophrenia:** <skit-suh-FREH-nee-uh>

Keywords: Antipsychotic, Aripiprazole, Schizophrenia, Long-acting injectable

What did the study look at?

What is schizophrenia?

Schizophrenia is a serious, long-term mental health condition that affects how a person thinks, acts, and expresses their emotions.

People with **schizophrenia** can experience symptoms of psychosis, like hallucinations, delusions, or unusual thoughts and behaviors. Other symptoms include social withdrawal or having less interest in activities, as well as problems with attention and memory.

[1]Department of Psychiatry and Behavioral Sciences, New York Medical College, Valhalla, NY, USA
[2]H. Lundbeck A/S, Valby, Denmark
[3]Otsuka Pharmaceutical Development & Commercialization Inc., Princeton, NJ, USA
[4]Otsuka Pharmaceutical Europe Ltd., Berkshire, UK

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Correspondence to:
Matthew Harlin, Otsuka Pharmaceutical Development & Commercialization Inc., Princeton, NJ, USA. Email: matthew.harlin@otsuka-us.com

Some people with **schizophrenia** have persistent symptoms. Other people have times with fewer or less intense symptoms, followed by a period where their symptoms get worse, known as a 'relapse'.

The symptoms of **schizophrenia** can negatively affect a person's day-to-day functioning, making it hard to carry out everyday tasks, work, and interact with other people.

How is schizophrenia treated?

People with **schizophrenia** are usually treated with a combination of medicine, psychotherapy (talking therapy), and community and family support.

Antipsychotics are a group of medicines that are used to treat people with **schizophrenia**. They help to manage symptoms of psychosis, like hallucinations or delusions.

Antipsychotics are available in many different forms, such as tablets, capsules, liquids, patches, and injections.

Some **antipsychotic** injections are short-acting, and are used when people require rapid relief of their symptoms. Other **antipsychotic** injections are long-acting, and are used to treat symptoms over a longer time period.

Long-acting **antipsychotic** products are injected in a muscle or under the skin and work by slowly releasing medicine into the bloodstream over a period ranging from 2 weeks to 6 months.

People treated with a long-acting injectable **antipsychotic** do not need to remember to take their medication every day.

What is aripiprazole injection every 2 months and how does it work?

Aripiprazole 2-month ready-to-use 960 mg (Ari 2MRTU 960 – **aripiprazole** injection every 2 months) is a long-acting injectable **antipsychotic** medicine that is used to treat adults with **schizophrenia** in the United States. Its brand name is **Abilify Asimtufii®**.

Aripiprazole injection every 2 months was developed to increase the number of medication choices available to people with **schizophrenia**.

Aripiprazole injection every 2 months comes in a syringe that has already been filled with an exact amount of medication. A healthcare professional injects the medicine into a person's buttock muscle once every 2 months (Figure 1).

The medicine's active ingredient is **aripiprazole**, an **antipsychotic** that modifies the activity of chemical messengers in the brain, such as dopamine and serotonin, which affect the way someone feels.

This helps to reduce symptoms in people with **schizophrenia**.

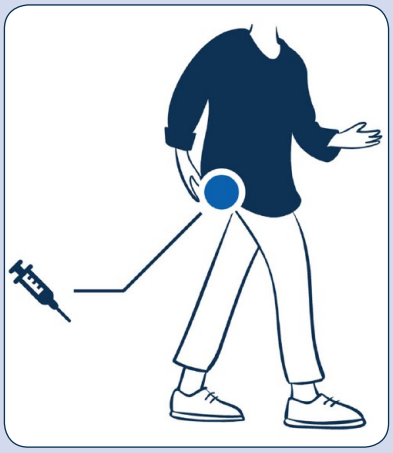

Figure 1. Aripiprazole injection every 2 months is injected into a person's buttock muscle.

What is the aripiprazole injection every 2 months study about, and what does this summary describe?

Aripiprazole once-monthly is an effective treatment for **schizophrenia** that has been available in the United States for more than 10 years. This medicine is known as Abilify Maintena®.

Before **aripiprazole** injection every 2 months was approved for use, people with **schizophrenia** could receive the once-monthly formulation.

The aim of this study was to confirm whether the **aripiprazole** injection every 2 months had a similar effect to **aripiprazole** once-monthly in people with **schizophrenia** or bipolar I disorder (another type of mental health disorder characterized by extreme mood swings, that shift from episodes of mania to episodes of depression).

To do this, researchers compared the **pharmacokinetics**, safety, tolerability, and efficacy (Figure 2) of the two different formulations over a period of 8 months.

Pharmacokinetics: How the body interacts with a medicine after it has been administered. It includes the movement of a medication into, through, and out of the body

Safety and tolerability: How much a medicine causes harm or undue risk

Efficacy: How well a medicine works

Figure 2. What did the study investigate?.

Where is this study in the drug development timeline?

Based on the information collected in the study, **aripiprazole** injection every 2 months was approved for use in the United States in April 2023, under the brand name **Abilify Asimtufii**®. It is used to treat adults with **schizophrenia** or bipolar I disorder.

Who took part in the study and what did it involve?

An overview of the study is provided below (Figure 3).

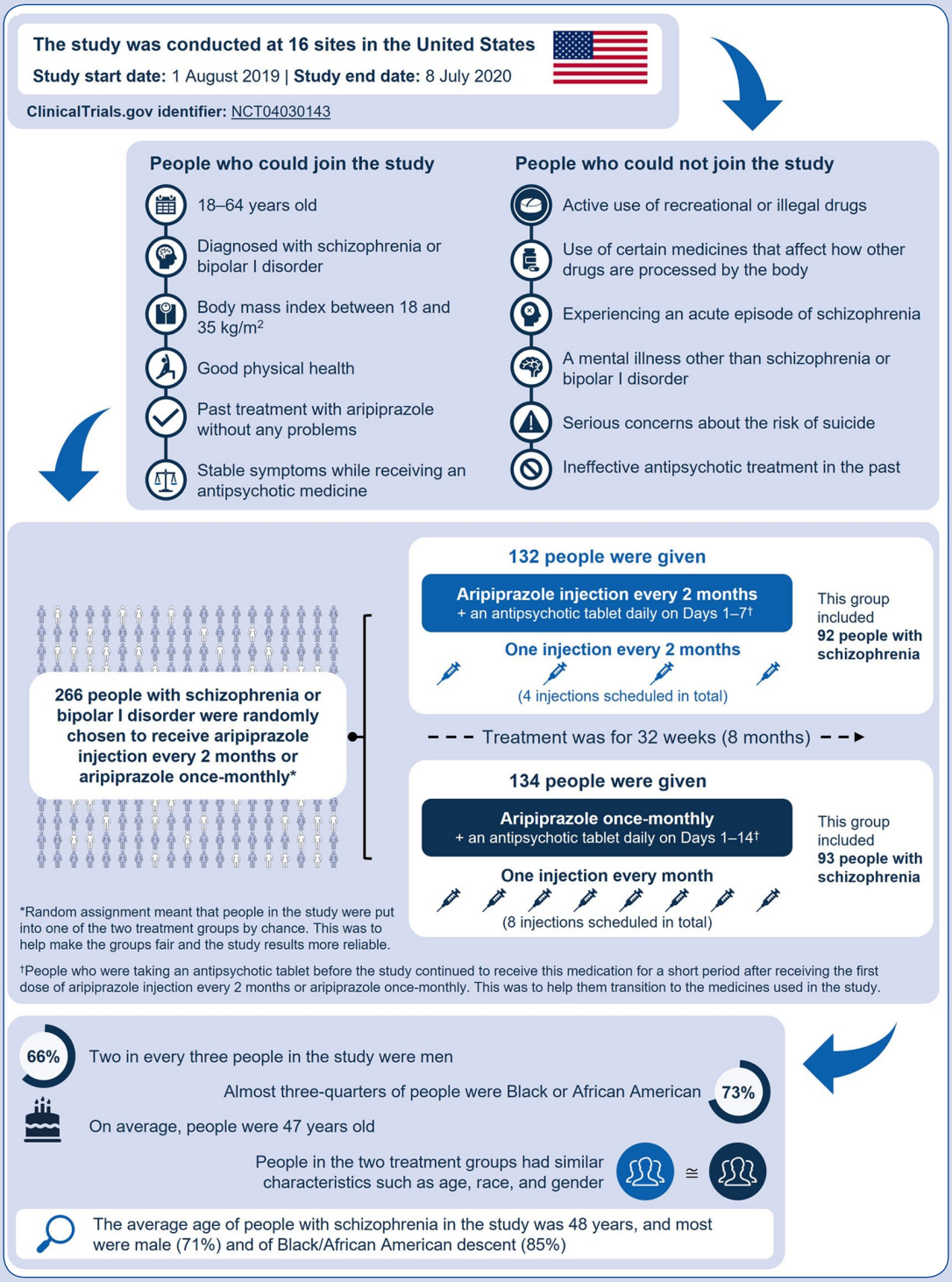

Figure 3. Study overview (further details are available at https://clinicaltrials.gov/study/NCT04030143).

What were the key results of the study?

Pharmacokinetics

A primary goal of the study was to measure the amount of **aripiprazole** in the blood, to see if it was the same during treatment with **aripiprazole** injection every 2 months or **aripiprazole** once-monthly.

This was assessed in all people in the study. It was done for two reasons:

- To see how much **aripiprazole** was present in the blood, since a certain level is needed for the medicine to be effective
- To check that **aripiprazole** was being gradually released into the bloodstream, resulting in steady and safe levels of the drug in the blood in the period between injections.

First, researchers looked at the concentration (amount) of **aripiprazole** in the blood on the last day of the study.

Results showed similar concentrations of **aripiprazole** in the blood 2 months (56 days) after the fourth (and last) dose of **aripiprazole** injection every 2 months and 1 month (28 days) after the eighth (and last) dose of **aripiprazole** once-monthly (Figure 4).

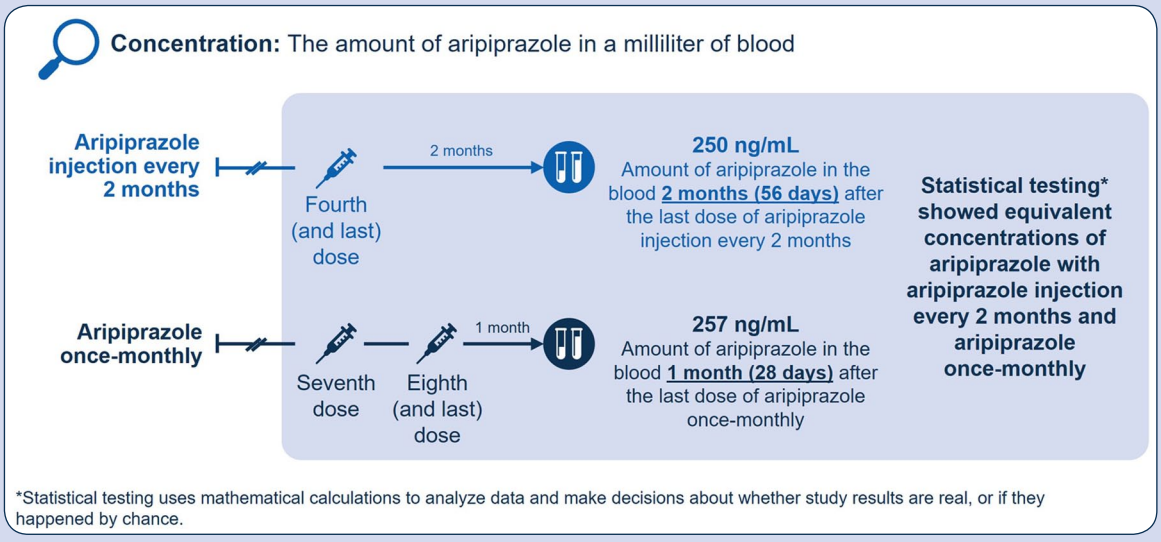

Figure 4. Concentrations of aripiprazole in the blood after the last dose of either treatment.

Next, researchers looked at exposure (amount the person received) to **aripiprazole** over a period of 2 months.

Results showed similar exposure to **aripiprazole** in the 2-month period following the last dose of **aripiprazole** injection every 2 months, and in the 1-month periods following the last two doses of **aripiprazole** once-monthly (Figure 5).

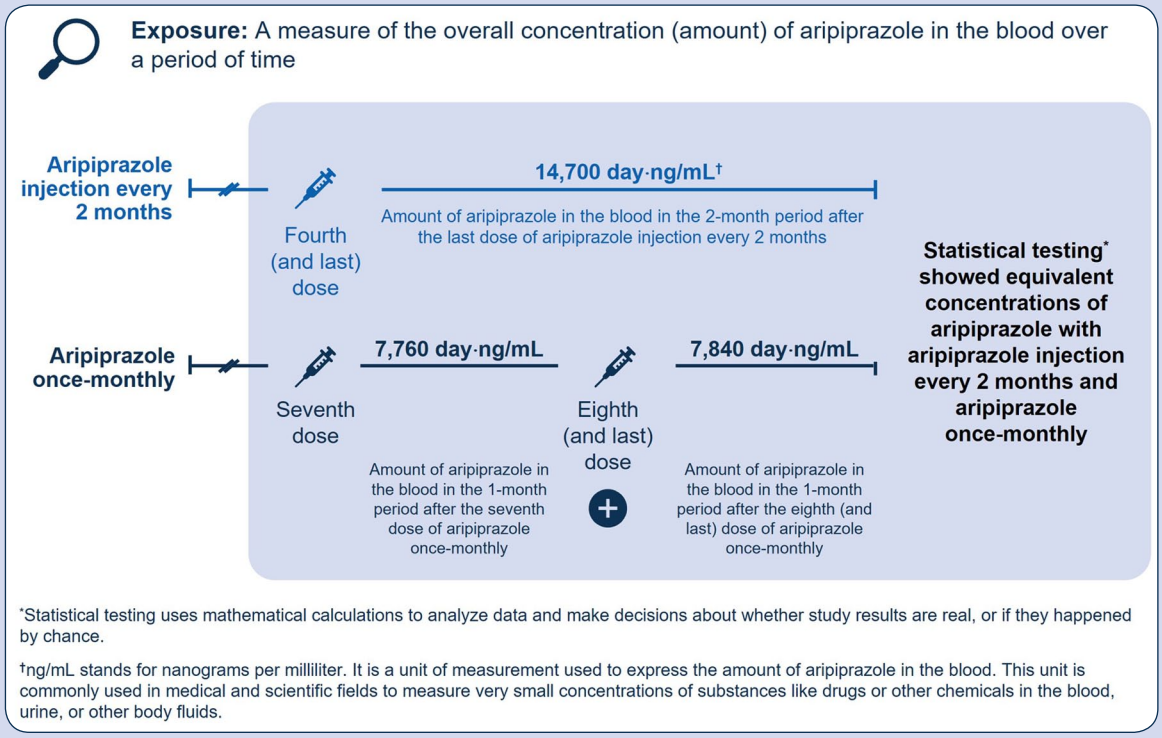

Figure 5. Exposure to aripiprazole from either treatment in the last 2 months of the study.

Over the whole study period, across multiple doses, the average concentration (amount) of **aripiprazole** in the blood was similar with **aripiprazole** injection every 2 months and **aripiprazole** once-monthly.

With both treatments, the average concentration of **aripiprazole** in the blood was almost always greater than 95 ng/mL. This is important since symptoms are more likely to get worse if the amount of **aripiprazole** in the blood falls below 95 ng/mL (Figure 6).

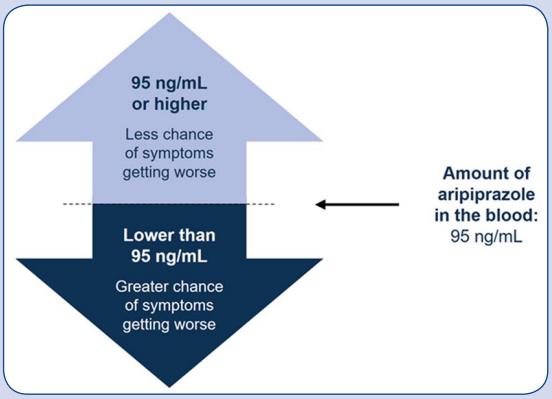

Figure 6. Risk of symptoms in relation to the amount of aripiprazole in the blood.

Safety and tolerability

Another primary goal of the study was to see if people had any adverse events (side effects) after receiving **aripiprazole** injection every 2 months.

- An adverse event is an unexpected medical problem that occurs in a person participating in a clinical study, after they have received the study medicine.
- An adverse event may or may not be caused by the study medicine.

People with **schizophrenia** who received **aripiprazole** injection every 2 months or **aripiprazole** once-monthly had a similar chance of experiencing side effects (Figure 7).

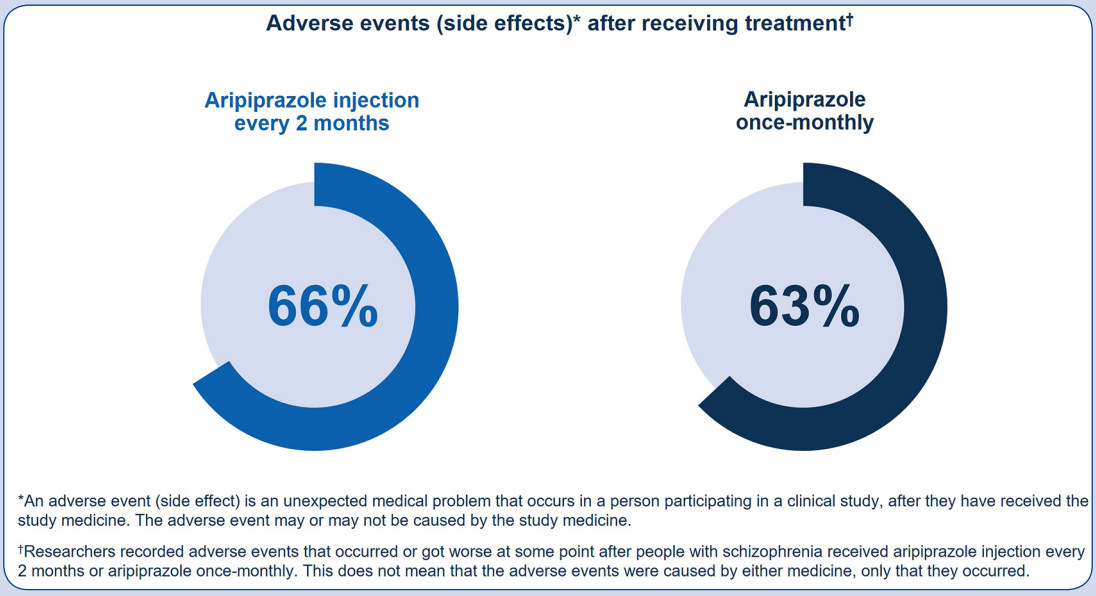

Figure 7. Adverse events experienced after receiving treatment.

With both medicines, most side effects happened after the first injection.

The study investigators mainly classified side effects as mild (some discomfort, which does not get in the way of a person's daily activities) or moderate (uncomfortable enough to affect a person's daily activities).

The most common side effects in people with **schizophrenia** who received **aripiprazole** injection every 2 months or **aripiprazole** once-monthly were (Figure 8):

- Weight gain
- Pain at the injection site
- **Akathisia** (feeling restless or having an intense urge to move)
- Insomnia (finding it difficult to fall or stay asleep).

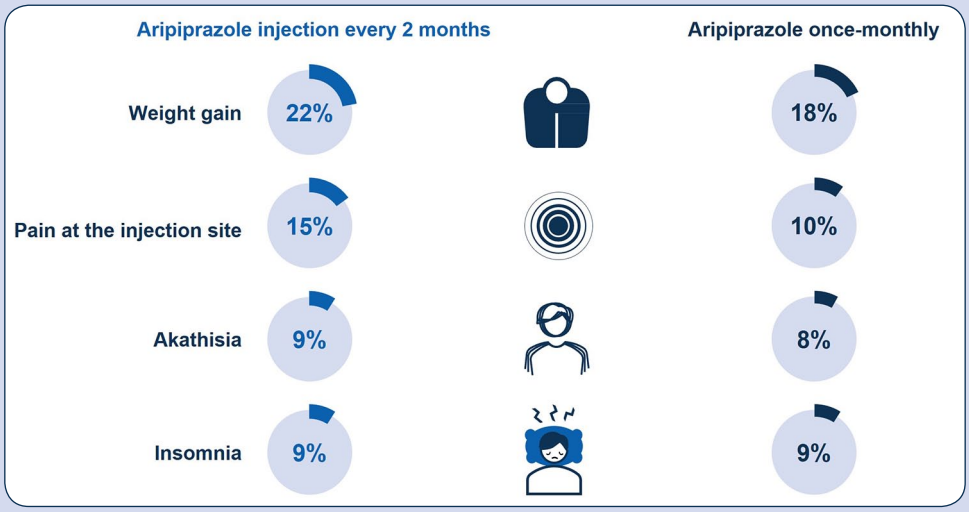

Figure 8. The most common side effects observed in the study.

Receiving an injection can make people anxious. They might be afraid of needles, or be worried that the injection will be painful or uncomfortable.

People with **schizophrenia** reported low levels of pain after receiving injections of **aripiprazole** every 2 months or **aripiprazole** once-monthly (Figure 9).

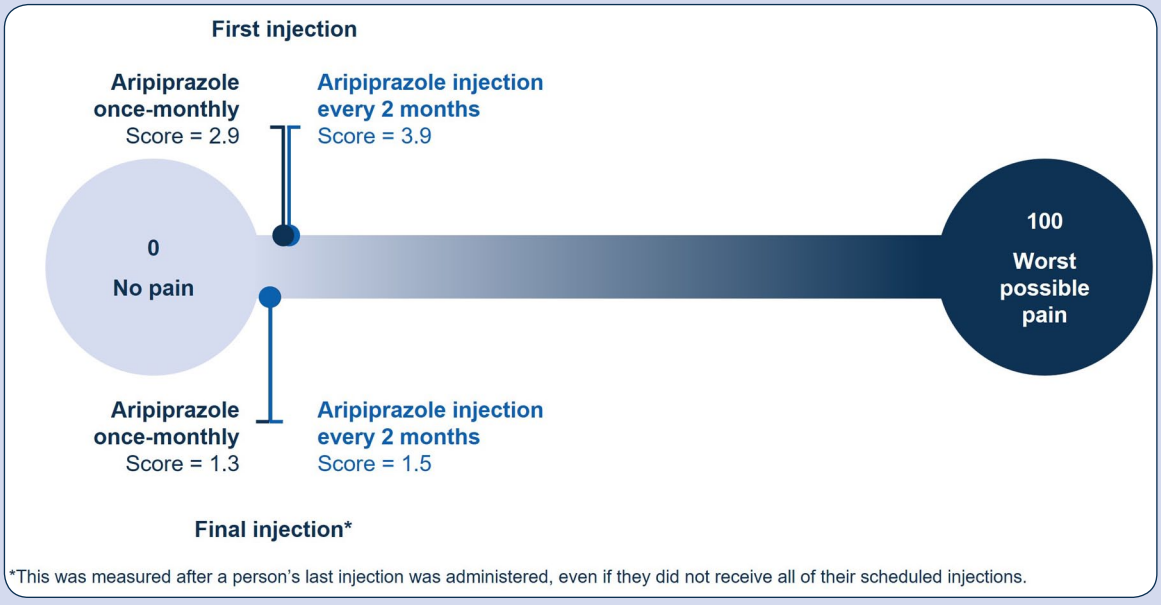

Figure 9. Injection site pain reported by people in the study.

According to the researchers, more than 9 in 10 people with **schizophrenia** had no pain or redness after their first or final injections of **aripiprazole** injection every 2 months or **aripiprazole** once-monthly. There were no cases of swelling or induration (hardening of the skin) after any injection.

Movement-related (or 'motoric') side effects can occur in people taking **antipsychotic** medicines. This can be a concern for people with **schizophrenia**.

In the study, motoric side effects occurred in 15% of people treated with **aripiprazole** injection every 2 months and 12% of people treated with **aripiprazole** once-monthly. The results of medical examinations showed no important changes in movement-related symptoms.

Efficacy

A secondary goal of the study was to see how well **aripiprazole** injection every 2 months maintained control of people's symptoms.

To do this, researchers used four questionnaires that measured how severe the symptoms of **schizophrenia** were, how much symptoms changed, and people's overall well-being (Figure 10).

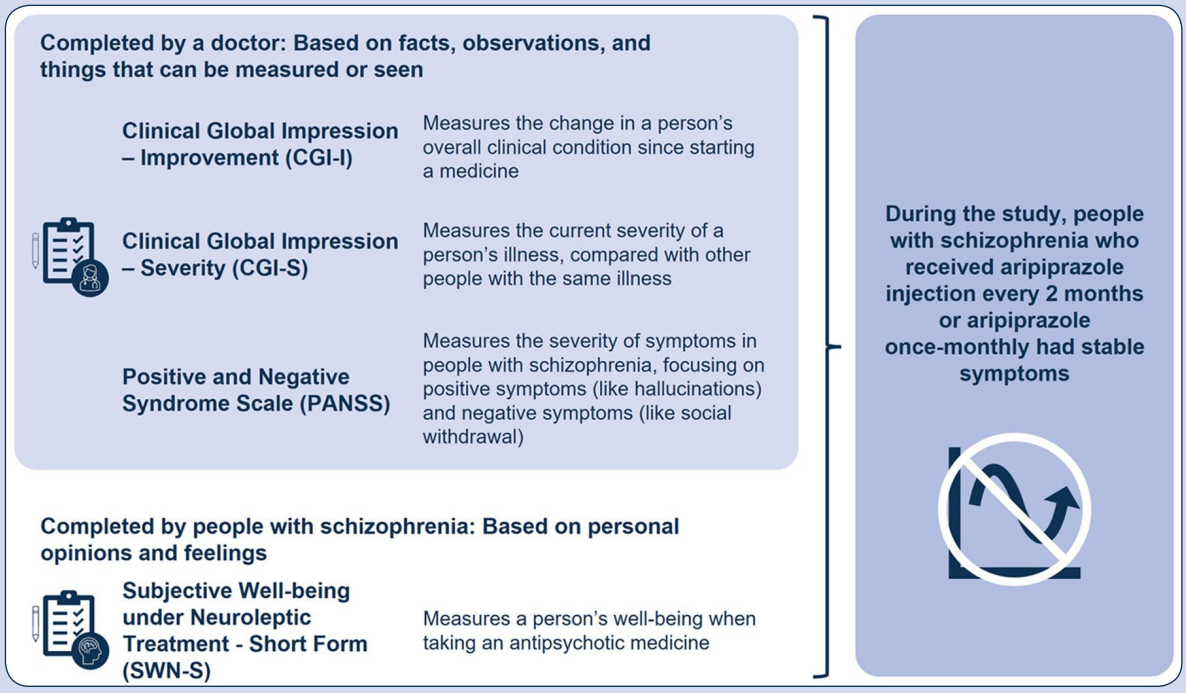

Figure 10. Questionnaires used to evaluate how well aripiprazole injection every 2 months maintained control of people's symptoms.

From the start to the end of the study, there was very little change in symptoms with **aripiprazole** injection every 2 months or **aripiprazole** once-monthly in people with **schizophrenia**. Researchers expected this outcome, since people were only allowed in the study if their symptoms were under control.

People had a generally positive attitude towards **antipsychotic** medicines at the start of the study. This did not change during treatment with **aripiprazole** injection every 2 months.

What were the main conclusions reported by the researchers?

Levels of **aripiprazole** in the blood were similar with **aripiprazole** injection every 2 months or **aripiprazole** once-monthly.

The chance of side effects with **aripiprazole** injection every 2 months or **aripiprazole** once-monthly in people with **schizophrenia** was similar, and both medicines were generally well tolerated.

Symptoms of **schizophrenia** remained stable with both treatments.

How could this study benefit people with schizophrenia?

Results from the study led to the approval of **aripiprazole** injection every 2 months in the United States. This has added to the number of medication choices that are available for people with **schizophrenia**.

People with **schizophrenia** might find **aripiprazole** injection every 2 months more convenient than some other **antipsychotic** medicines, since it only needs to be given once every 2 months.

Based on separate research, receiving injections less often could have several benefits. It might make it easier for people to keep up with their treatment, and could mean their symptoms are more stable. Receiving treatment less often could also make things easier for caregivers and family.

People with **schizophrenia** may need to take treatment for several years, especially if they have had multiple periods where their symptoms are not under control. The length of time that a person with **schizophrenia** might receive treatment with **aripiprazole** injection every 2 months will depend on their needs and how they respond to treatment.

Who might find this summary helpful?

People who may find this summary helpful include those living with **schizophrenia** and their family, patient advocates and patient groups, and healthcare professionals who treat people with **schizophrenia**.

How to use this summary to help people and doctors talk about this research

- **Question from a person with schizophrenia to their doctor:** How important is this research to my care?
- **Question from a doctor to a person with schizophrenia:** How relevant is this research to what matters most to you?

Are there any plans for further studies?

The **aripiprazole** injection every 2 months is now being used in clinical practice. Information on how the medicine works in the real world will be collected and published at a later date. This will provide insight into its use in situations not covered in the study. Examples include people who have additional illnesses or who are taking extra medicines.

Who sponsored this study?

This study was sponsored by Otsuka Pharmaceutical Development & Commercialization Inc. and H. Lundbeck A/S, who are the developers and manufacturers of **aripiprazole** injection every 2 months and **aripiprazole** once-monthly. The two companies gave money and support to help carry out the study and find out more about the medicines being tested.

- Otsuka Pharmaceutical Development & Commercialization Inc.
  508 Carnegie Center Dr
  Princeton, NJ 08540
  United States
  Phone (United States): +1 609-524-6788
- H. Lundbeck A/S
  Ottiliavej 9
  2500 Valby
  Denmark
  Phone (Denmark): +45 3630 1311

The sponsors thank everyone who took part in the study.

Disclaimers

Aripiprazole injection every 2 months is a long-acting injectable **antipsychotic** that is approved for use in adults with **schizophrenia** or bipolar I disorder in the United States.

This summary reports the results of a single study that examined the **pharmacokinetics**, safety, and efficacy of **aripiprazole** injection every 2 months in people with **schizophrenia** or bipolar I disorder. The summary reports **pharmacokinetic** outcomes in all people in the study, and safety and efficacy outcomes in those people in the study who had **schizophrenia**.

The results of the study may be different to other studies that researchers have conducted in the past.

The results reflect outcomes in a selected group of people enrolled in a clinical study, and may not apply to all people with **schizophrenia**.

Healthcare professionals must look at the results of many types of studies to understand whether a drug works, how it works, and whether it is safe to prescribe.

Further information

More information about the trial can be found at: https://www.clinicaltrials.gov/study/NCT04030143.

The results summarized here were published in two different articles: one describing outcomes in people with **schizophrenia** or bipolar I disorder, and another describing outcomes in people with **schizophrenia** only.

The original article describing outcomes in adults with schizophrenia or bipolar I disorder is called 'A randomized, open-label, multiple-dose, parallel-arm, pivotal study to evaluate the safety, tolerability, and pharmacokinetics of aripiprazole 2-month long-acting injectable in adults with **schizophrenia** or bipolar I disorder'.

- You can find the full article, as well as supplementary information, here: https://link.springer.com/article/10.1007/s40263-023-00996-8.
- You can access the full article and the supplementary information for free.

The original article describing outcomes in adults with schizophrenia only is called 'Safety and efficacy of aripiprazole 2-month ready-to-use 960 mg: secondary analysis of outcomes in adult patients with schizophrenia in a randomized, open-label, parallel-arm, pivotal study'.

- You can find the full article, as well as supplementary information, here: https://www.psychiatrist.com/jcp/safety-efficacy-aripiprazole-2-month-ready-to-use-960-mg/.
- You can access the full article and the supplementary information for free.

An article describing study outcomes in people with bipolar I disorder can be found here:

- https://www.tandfonline.com/doi/full/10.1080/03007995.2023.2219155.
- You can access the full article for free.

An article demonstrating that symptoms are more likely to get worse if the amount of **aripiprazole** in the blood falls below 95 ng/mL can be found here:

- https://accp1.onlinelibrary.wiley.com/doi/10.1002/cpdd.1022.
- You can access the full article for free.

An article on the possible benefits of choosing an **antipsychotic** medicine that is injected less frequently can be found here:

- https://www.tandfonline.com/doi/full/10.1080/03007995.2023.2287612.
- You can access the full article for free.

More information about clinical trials in general can be found at: https://www.clinicaltrials.gov/study-basics/learn-about-studies.

Further educational resources

- American Psychiatric Association (APA) website: https://www.psychiatry.org/.
- National Institute of Mental Health (NIMH) webpage about schizophrenia: https://www.nimh.nih.gov/health/topics/schizophrenia.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the International Council for Harmonization Good Clinical Practice guidelines and local regulatory requirements. The study protocol was approved by the governing institutional review board (IRB) or independent ethics committee for each investigational site. Participating sites were within the United States and utilized the central IRB Advarra. Advarra IRB approved each site by issuing a dated approval letter. Each site was approved by Advarra IRB prior to the site initiation visit and prior to screening potential participants. All patients provided written informed consent prior to the start of the study.

Consent for publication

Not applicable.

Author contributions

Leslie Citrome: Formal analysis; Writing – original draft; Writing – review & editing.

Pedro Such: Formal analysis; Writing – original draft; Writing – review & editing.

Murat Yildirim: Formal analysis; Writing – original draft; Writing – review & editing.

Jessica Madera-McDonough: Formal analysis; Writing – original draft; Writing – review & editing.

Clodagh Beckham: Formal analysis; Writing – original draft; Writing – review & editing.

Na Jin: Formal analysis; Writing – original draft; Writing – review & editing.

Suzanne Watkin: Formal analysis; Writing – original draft; Writing – review & editing.

Zhen Zhang: Formal analysis; Writing – original draft; Writing – review & editing.

Frank Larsen: Conceptualization; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

Matthew Harlin: Conceptualization; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

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Competing interests

Leslie Citrome has served as consultant to AbbVie/Allergan, Acadia, Adamas, Alkermes, Angelini, Astellas, Avanir, Axsome, BioXcel, Boehringer Ingelheim, Cadent Therapeutics, Cerevel, Clinilabs, COMPASS, Eisai, Enteris BioPharma, HLS Therapeutics, Idorsia, Impel, INmune Bio, Intra-Cellular Therapies, Janssen, Karuna, Lundbeck, Lyndra, Marvin, Medavante-ProPhase, Merck, Mitsubishi-Tanabe Pharma, Neurelis, Neurocrine, Novartis, Noven, Otsuka, Ovid, Praxis, Recordati, Relmada, Reviva, Sage, Sunovion, Supernus, Teva, University of Arizona, and Vanda, and has done one-off *ad hoc* consulting for individuals/entities conducting marketing, commercial, or scientific scoping research. He has served as speaker for AbbVie/Allergan, Acadia, Alkermes, Angelini, Axsome, BioXcel, Eisai, Idorsia, Intra-Cellular Therapies, Janssen, Lundbeck, Neurocrine, Noven, Otsuka, Recordati, Sage, Sunovion, Takeda, and Teva, and contributed to CME activities organized by medical education companies such as Medscape, NACCME, NEI, Vindico, and universities and professional organizations/societies. He holds a small number of shares of common stock with Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Merck, and Pfizer (purchased >10 years ago). He currently has options for acquiring stocks with Reviva. He has received royalties or income from publishing from Taylor & Francis (Editor-in-Chief, Current Medical Research and Opinion, 2022–date), Wiley (Editor-in-Chief, International Journal of Clinical Practice, through end 2019), UpToDate (reviewer), Springer Healthcare (book), and Elsevier (Topic Editor, Psychiatry, Clinical Therapeutics). Matthew Harlin, Na Jin, Suzanne Watkin, and Zhen Zhang are full-time employees of Otsuka Pharmaceutical Development & Commercialization Inc. At the time of the study, Jessica Madera-McDonough was a full-time employee of Otsuka Pharmaceutical Development & Commercialization Inc. Clodagh Beckham is a full-time employee of Otsuka Pharmaceutical Europe Ltd. Frank Larsen, Pedro Such, and Murat Yildirim are full-time employees of H. Lundbeck A/S.

Availability of data and materials

To submit inquiries related to Otsuka clinical research, or to request access to individual participant data (IPD) associated with any Otsuka clinical trial, please visit https://clinical-trials.otsuka.com/. For all approved IPD access requests, Otsuka will share anonymized IPD on a remotely accessible data sharing platform.

ORCID iD

Leslie Citrome https://orcid.org/0000-0002-6098-9266