This is a summary of a clinical study in children with cancer. It is written for the general reader and uses language that is easy to understand. It includes information about how researchers did the study and what the results were. The simplified title for the study is: 'A study to identify the best dose of volasertib in children with acute leukaemia or advanced solid tumours'.

We thank all patients, and the parents of patients, who took part in this study. Through your participation, you helped researchers answer important questions about volasertib and the treatment of cancer in children.

What was this study about?

Researchers wanted to find the highest dose of the medicine volasertib that children with cancer could tolerate. This dose would be used in future studies of childhood acute leukaemia and solid tumours. The patients in this study were either children with acute leukaemia or children with advanced solid tumours, for whom no effective treatment was known. Researchers also collected information on the unwanted effects of volasertib.

This study started in October 2013 and finished in February 2017. The sponsor of this study was Boehringer Ingelheim.

Why was the study needed?

New treatments for childhood acute leukaemia and advanced solid tumours in children are needed. Treatments for childhood acute leukaemia have improved greatly over the past 50 years. However, new treatments are needed for children whose cancers resist available treatments or return after treatment. In addition, the current standard treatments for both acute leukaemia and advanced solid tumours have severe medicine-related side effects in children. Novel treatments with fewer side effects are needed.

Volasertib is a potential new medicine for childhood acute leukaemia and solid tumours. Before researchers can check if a new medicine works, they must first learn what the highest dose is that the patients can take before unwanted effects become too serious.

Which medicines were studied?

Volasertib (BI 6727) is a new medicine which is given by infusion into a vein. It works by blocking the ability of cancer cells to grow and spread throughout the body. Volasertib has already been studied as a treatment for adults with cancer.

Who participated in the study?

Children with 2 types of cancer could take part in this study:

- Children with acute leukaemia who had already had at least 2 intensive treatments with no lasting success
- Children with advanced solid tumours for which no treatment was known

Overall, 22 patients were treated in this study. The patients were put into 2 age groups:

Patients aged 2 to less than 12 years. There were 12 patients in this age group. Four patients had acute leukaemia and 8 had solid tumours. In this group, the average age was 8 years. The youngest patient was 2 years old and the oldest patient was 11 years old. Half of this age group were boys and half were girls.

Patients aged 12 to less than 18 years. There were 10 patients in this age group. Three patients had acute leukaemia and 7 had solid tumours. In this group, the average age was 15 years. The youngest patient was 12 years old and the oldest patient was 17 years old. There were 8 boys and 2 girls in this age group.

Patients participated in the study in 7 countries in Europe: Austria, Belgium, Czech Republic, France, Germany, Italy, and the United Kingdom.

How was this study done?

Researchers wanted to know the highest dose of volasertib that patients in each age group could tolerate. To find this dose, doctors gave increasing doses of volasertib to different small groups of patients. They checked each group for certain severe unwanted effects. They determined the dose at which no more than 1 out of 6 patients had such unwanted effects. This dose was the maximum tolerated dose. It was determined in the first treatment cycle, which took 2 weeks in this study.

Both the study doctor and the patients knew what dose the patients were getting. Patients were given volasertib as an infusion into a vein for about an hour once every 2 weeks.

Patients in each age group were assigned to volasertib dose groups by age and order of entering the study. In each age group, the starting dose was 200 milligrams (mg) per square metre (m^2) of body surface area.

Patients could continue on treatment cycles of volasertib until they had unwanted effects that they could not tolerate or until their cancer got worse.

All patients followed the same procedures:

- The patients and their parents visited the doctor about every 5 days.
- At these visits, blood was collected for safety tests, heart rhythm was measured, and patients and/or their parents answered questions about their health.
- At some visits, the size of their tumour was measured or their bone marrow (the spongy tissue in the centre of bones) was checked.
- At all visits, the doctors collected information on unwanted effects.

The doctors looked after each patient and checked their test results. The doctors did more medical tests when needed.

What were the results of this study?

In the age group of 2 years to less than 12 years, the patients took volasertib doses up to 300 mg/m^2. No patient had a severe unwanted effect that would indicate that the dose was too high. A safety committee decided to stop dose increases beyond 300 mg/m^2, as patients did not show signs of disease improvement that would justify further dose increases. Therefore, the recommended dose for this age group was found to be 300 mg/m^2.

In the age group of 12 years to less than 18 years, the maximum tolerated dose was determined to be 200 mg/m^2.

What unwanted effects did patients have?

In the age group of 2 years to less than 12 years, 10 of 12 patients (83%) had at least 1 unwanted effect.

The table below shows the unwanted effects that occurred in at least 2 patients in this age group.

Doctors keep track of all health problems patients have during a study. Some of these health problems might be caused by the study medicines, and some by other medicines taken by the patient. Others might be caused by the disease, and some have yet a different cause. Here we describe health problems that the doctors thought were caused by the study medicines. These health problems are called unwanted effects.

Age Group: **2 years to less than 12 years**	**Volasertib** **12 patients**
Patients with any unwanted effect	10 patients (83%)
Low level of red blood cells (anaemia)	5 patients (42%)
Fever with low level of a type of white blood cell (febrile neutropenia)	5 patients (42%)
Low level of a type of white blood cell (neutropenia)	5 patients (42%)
Low level of tiny blood cells that help form clots (thrombocytopenia)	4 patients (33%)
Low level of white blood cells (leukopenia)	2 patients (17%)
Low level of sodium in blood (hyponatraemia)	2 patients (17%)
Fever (pyrexia)	2 patients (17%)
Lower level of a type of white blood cell (lymphocyte count decreased)	2 patients (17%)
Lower level of tiny blood cells that help form clots (platelet count decreased)	2 patients (17%)
Lower level of all white blood cells (white blood cell count decreased)	2 patients (17%)

In the age group of 12 years to less than 18 years, 9 of 10 patients (90%) had at least 1 unwanted effect. The table below shows the unwanted effects that occurred in at least 2 patients in this age group.

Age Group: 12 years to less than 18 years	**Volasertib 10 patients**
Patients with any unwanted effect	9 patients (90%)
Low level of tiny blood cells that help form clots (thrombocytopenia)	4 patients (40%)
Low level of red blood cells (anaemia)	4 patients (40%)
Fever with low level of a type of white blood cell (febrile neutropenia)	3 patients (30%)
Low level of a type of white blood cell (neutropenia)	3 patients (30%)
Low level of white blood cells (leukopenia)	2 patients (20%)
Headache	2 patients (20%)
Vomiting	2 patients (20%)
Itchy skin (pruritus)	2 patients (20%)
Muscle pain (myalgia)	2 patients (20%)
Weakness (asthenia)	2 patients (20%)
Fever (pyrexia)	2 patients (20%)
Increased liver enzymes (alanine aminotransferase increased)	2 patients (20%)
Abnormal heart rhythm (electrocardiogram QT prolonged)	2 patients (20%)
Lower level of a type of white blood cell (lymphocyte count decreased)	2 patients (20%)
Lower level of a type of white blood cell (neutrophil count decreased)	2 patients (20%)
Lower level of tiny blood cells that help form clots (platelet count decreased)	2 patients (20%)
Lower level of all white blood cells (white blood cell count decreased)	2 patients (20%)

Some patients in the study had serious unwanted effects. An unwanted effect was serious if it caused the patient to go to the hospital or stay longer in the hospital. It was also serious if it needed a doctor's immediate attention, was life-threatening, or caused death.

Overall, 11 of 22 patients (50%) had at least 1 serious unwanted effect that doctors thought was related to the study medicine. These serious unwanted effects were as follows:

- Bleeding in the brain (intracranial haemorrhage)
- Abnormal heart rhythm (electrocardiogram QT prolonged)
- Sore, pus-filled area on the neck (neck abscess)
- Low level of red blood cells (anaemia)
- Fever with low level of a type of white blood cell (febrile neutropenia)
- Low level of white blood cells (leukopenia)
- Low level of tiny blood cells that help form clots (thrombocytopenia)
- Bleeding in the gastrointestinal tract (gastrointestinal haemorrhage)
- Weakness (asthenia)
- Bone marrow not producing blood cells (bone marrow toxicity)
- Low level of a type of white blood cell (neutropenia)
- Headache
- Diarrhoea
- Abdominal pain
- Vomiting
- Muscle pain (myalgia)

Five patients died while on study treatment. One of these patients died due to bleeding in the brain (intracranial haemorrhage) that study doctors thought was related to the study medicine. The study doctors thought that the other 4 deaths were not related to the study medicine.

Are there follow-up studies?

No follow-up studies are planned.

Where can I find more information?

You can find the scientific summaries of the study results at these websites:

www.trials.boehringer-ingelheim.com	search for the study number: 1230.27
www.clinicaltrialsregister.eu	search for the EudraCT number: 2013-001291-38
www.clinicaltrials.gov	search for the NCT number: NCT01971476

The full title of the study is:

'Open, non-controlled, dose escalating Phase I trial to evaluate the pharmacokinetics, pharmacodynamics, tolerability, and toxicity of volasertib in paediatric patients from 2 years to less than 18 years of age with acute leukaemia or advanced solid tumour, for whom no effective treatment is known'.

Important notice

This summary shows only the results from one study and may not represent all of the knowledge about the medicine studied. Usually, more than one study is done to find out how well a medicine works and the side effects of the medicine. Other studies may have different results.

You should not change your child's therapy based on the results of this study without first talking to your child's physician. Always consult your child's physician about your child's specific therapy.

Boehringer Ingelheim has provided this lay summary in accordance with transparency obligations. This lay summary is intended for audiences located within the European Union.