Trial title	A trial to evaluate whether encorafenib in combination with binimetinib is effective and safe in participants with high risk Stage II BRAF-mutated melanoma
Disease	Stage IIB/IIC (high risk) *BRAF* V600 E/K Melanoma Melanoma is classified into different stages (I, II, III, IV) depending on the size of the tumor and how much the cancer has spread. In Stage II melanoma, the cancer cells are in both the first layer of skin—the epidermis—and the second layer of skin—the dermis. The stage II melanoma is higher risk than stage I, either due to higher depth of tumor or presence of ulceration.There is no evidence the cancer has spread beyond the area of the skin where it began and melanoma was completely surgically removed, but patients stage II pose a higher risk their melanoma relapses or comes back as metastases There are three subgroups of Stage II melanoma : IIA -IIB – IIC, the two latest ones having statistically a higher risk to develop metastases.
Treatment	Encorafenib (BRAFTOVI®) in combination with binimetinib (MEKTOVI®) for a maximum of 12 months
Participants	Subject aged 18 years or older with High risk stage II BRAF V600E/K melanoma
Trial dates	From 18 May 2022 (first participant first visit) to May 2035 (anticipated end of trial), anticipated primary completion date (31 March 2027)
Trial Locations	Europe (Austria, Belgium,Czech Republic, France ,Germany, Greece – Hungary, Italy, Norway, Poland, Portugal , Spain , Sweden and

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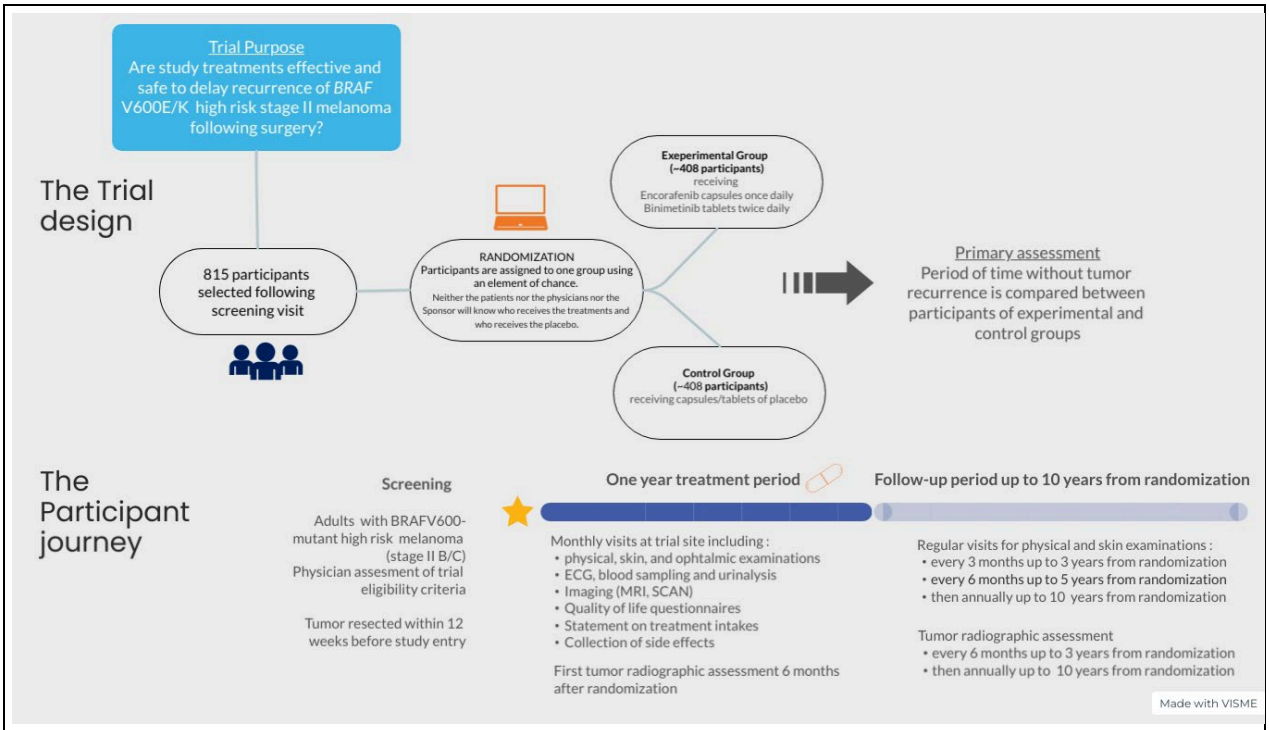
	Netherlands), Australia, Argentina, Brazil, Canada, Israel, South Africa, Switzerland, Serbia and United Kingdom
We do research to learn the best ways to help patients. This trial will help us to answer important questions about adjuvant treatment of Melanoma	

This document is a brief summary of a clinical trial protocol. It is written in plain language for the general public, providing answers to the following questions:

- What is the purpose of the trial?
- What are the objectives of the trial and how are they evaluated?
- How is the trial conducted?
- Who can take part in the trial?
- What are the trial treatments and how are they administered?
- What are the possible benefits and risks in taking part in the trial?

What is the purpose of the trial?	The COLUMBUS-AD is a Phase III clinical trial designed to evaluate how effective and safe a BRAF/MEK inhibitor combination therapy is at preventing melanoma returning (local relapse) or spreading to a distant area (metastasis) in comparison to placebo. The trial addresses to patients with high-risk stage II (IIB/IIC) *BRAF* V600E/K melanoma soon after their tumors are completely removed by surgery. The BRAF inhibitor that will be used in the study is called encorafenib, and the MEK inhibitor is called binimetinib.
What are the objectives of the trial and how are they evaluated?	The main objective will be to evaluate whether treatment with encorafenib and binimetinib prolongs the period of time without recurrence after melanoma has been removed by surgery (recurrence-free survival RFS) as compared to placebo in patients with stage IIB/C *BRAF* V600E/K melanoma. In addition, the trial will allow to: -Assess whether the treatment with encorafenib and binimetinib prolongs the period of time without the skin tumor could spread in the body as compared to placebo (distant metastasis free

	survival(DMFS)) and prolongs the period of time between treatment assignment and the participant death (overall survival (OS)) -Assess the participant quality of life during the treatment -Assess the safety and tolerability of the treatment by collecting the frequency and type of side effects that occurred in participants all along the trial and the degree to which overt side effects will be tolerated by the participant
How is the trial conducted?	This trial is a triple blind randomized Phase III trial. Approximately 815 participants aged 18 years and more, will join the study around the world. Through the randomization process, ie. using an element of chance, participant will be assigned to a study group: receiving either the encorafenib and binimetinib (experimental group) or their respective placebos (control group). There is a one in two chance of getting the encorafenib and binimetinib, and a one in two chance of getting their placebos. The study treatments (encorafenib and binimetinib combination or their placebos) will be administrated for a maximum duration of 12 months. During this period, there will be regular monthly visits to the study site. After the treatment period, Participants will have to come back to the study site for a safety follow-up visit, approximately 30 days after the last dose of study treatment and to continue to perform clinical and imaging exams to follow the evolution of their melanoma for up to 10 years. The scheme summarizes the information presented above:



Who can take part in the trial?	To be part of the trial, participant must fulfill several conditions including the following: • Be aged 18 years or older with high risk melanoma (Stage IIB/C) • Had recent (<12 weeks) surgery to completely remove the melanoma (resection) • The tumor has a specific genetic mutation (*BRAF V600E/K*) called BRAF mutation • Do not be pregnant, lactating or breast-feeding women
What are the trial treatments and how are they administered ?	<table><tr><td>Treatment</td><td>Encorafenib (BRAFTOVI®)</td><td>Binimetinib (MEKTOVI®)</td></tr><tr><td>Dose</td><td>450 mg (6 x 75 mg)</td><td>45mg (3x15mg)</td></tr><tr><td>Frequency</td><td>Once a day</td><td>Twice a day</td></tr><tr><td>Route of administration</td><td>Oral (capsule)</td><td>Oral (tablet)</td></tr></table> For participants randomized to the control arm, they will receive encorafenib and binimetinib placebos

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	Duration of administration: 12 months but treatment could be stopped before if melanoma recurs (re-appears at the initial disease site, a nearby area or an area distant from the original site) or if the treatment is not tolerated.
What are the possible benefits and risks in taking part in the trial?	The combination of encorafenib and binimetinib is effective and the safety profile is well known and generally manageable in patients with advanced melanoma (stage III and IV) whose tumor harbor the *BRAF* V600 mutation. This combination was approved by Health Authorities for this specific use and is commercialized in several countries around the world such as in European Union countries, Australia and the United States. Based on the activity observed in patients with metastatic melanoma and considering the high risk of relapse for patients with a stage IIB/C melanoma there is the potential for this combination to be efficacious in the earlier stages, in the adjuvant setting. Participation into this trial might increase the burden of melanoma care in terms of the amount of visits and imaging compared to the local / national guidelines for stage II melanoma. Also the trial is randomized and 50% of patients will receive placebo. Moreover, participants will also need to have more blood drawn than in an active surveillance protocol. Of course, the largest burden and risk for participants is to develop side effects due to the encorafenib & binimetinib treatment, for which participants are informed by trial doctors at study entry and are closely monitored for all the duration of the trial.

Cinical Trial identification

Protocol Number	W00090GE303_ EORTC 2139_MG
Protocol Version	2.0 dated 22 July 2022
Full trial title	**Adjuvant encorafenib & binimetinib vs. placebo in resected stage II BRAF V600E/K mutated melanoma: a randomized triple-blind Phase III Study in collaboration with the EORTC Melanoma Group.**
Registry ID	ClinicalTrials.gov: NCT05270044 EudraCT Number: 2021-004310-19

Who sponsors this trial?

Name and contact details of the sponsor	Pierre Fabre Médicament Les Cauquillous 81500 Lavaur-France .

Additional Information

This trial is conducted in collaboration with the European Organisation for Research and Treatment of Cancer – EORTC

EORTC is an independent, non-governmental, non-profit cancer research Organisation established under the laws of Belgium, its mission is to coordinate and conduct international translational and clinical research to improve the standard of cancer treatment for patients. In addition to independence, EORTC is recognised for scientific and methodological rigor bringing robust datasets to doctors and patients for therapeutic improvement. EORTC covers all disciplines to fight against cancer. EORTC research leaves no one behind and addresses all patients, including patients with rare tumours and specific patient populations.

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Glossary	
Adjuvant	A treatment whose objective it is to prevent or stop the spread of cancer to other parts of the body. Often used after surgical removal of the primary lesion. These can include chemotherapy, immunotherapy, radiation, and vaccine therapy. Adjuvant therapy is often used after primary treatments, such as surgery, to lessen the chance of the cancer coming back. Even if the surgery was successful at removing all visible cancer, microscopic bits of cancer sometimes remain and are undetectable with current methods
BRAFV600E	All humans have a gene called BRAF which is responsible for sending signals to proteins called B-Raf inside of cells that help them grow. In some melanoma patients, this gene mutates and causes cancer cells to grow in uncontrolled ways
BRAF/MEK inhibitor	BRAF inhibitor and MEK inhibitor are drugs which may turn off the effect of the BRAF mutation, each acting in a different way
Placebo	A placebo is an inactive substance or other intervention that looks the same as, and is given the same way as, an active drug or treatment being tested.
Melanoma	Melanoma is a type of skin cancer that occurs when pigment-producing cells—known as melanocytes—mutate and become cancerous. Staging is defined by the characteristics of the original (primary) melanoma tumor and if/how far it has spread in your body. Melanoma is divided into stages using five Roman numerals (0 through IV) and up to four letters (A through D) that indicate a higher risk within each stage.
Metastatic melanoma	Once skin cancer spreads beyond the lymph nodes nearest the primary tumor, it has ravelled to a 'distant site.' A distant site may be an internal organ, skin not near the primary tumor, or lymph nodes other than those closest to the primary tumor.
RFS	The length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of that cancer. In a clinical trial, measuring the RFS is one way to

	see how well a new treatment works. Also called DFS, disease-free survival, and relapse-free survival.
DMFS	The length of time from the start of treatment for cancer that a patient is still alive and the cancer has not spread to other parts of the body. In a clinical trial, measuring the DMFS is one way to see how well a new treatment works..
Side effects	Side effects are unwanted medical events (such as headache) that happen during the trial and that are related or possibly related to trial treatment.
Overalll survival (OS)	The length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive. In a clinical trial, measuring the OS is one way to see how well a new treatment works.
Phase III trials	This phase expands the drug or treatment testing to hundreds, sometimes thousands, of people. Some patients receive the new, or experimental, treatment alone or in combination with the standard of care. The goal is to provide data on efficacy, safety and side effects. The information from Phase III studies is often required to gain regulatory approval from Health Authorities like the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA).
Randomization	Randomization is the assignment to one of the treatment groups using an element of chance