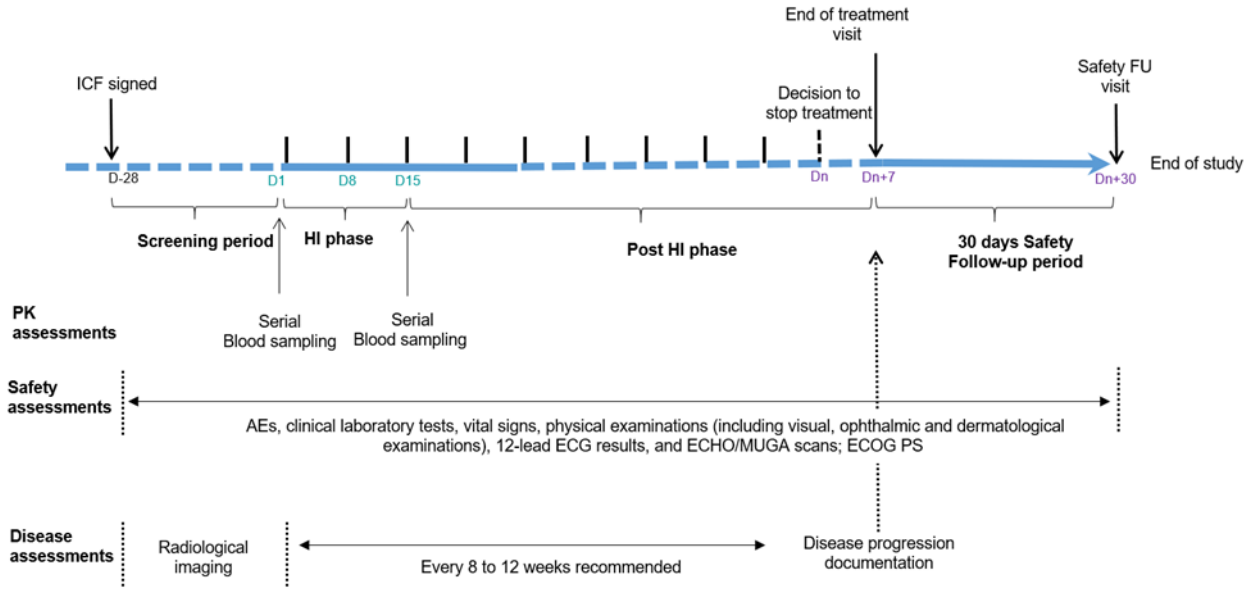
Trial title	A trial to evaluate the impact of liver dysfunction on elimination of encorafenib in combination with binimetinib administered to patients with *BRAF*^{V600E}–mutant solid tumors
Disease 	Unresectable or metastatic *BRAF*^{V600E}–mutant solid tumors
Treatment 	Encorafenib (BRAFTOVI®) in combination with binimetinib (MEKTOVI®)
Participants 	Adults' participants with *BRAF*^{V600E}–mutant solid tumors with or without liver dysfunction
Trial dates 	From 30 May 2022 (first participant entering the trial) to December 2023 (estimated end of trial)
Trial Locations 	Spain, Italy and Czech Republic
We do research to improve patient care. This trial will help us to answer important questions about treatment of BRAF V600-mutant solid tumors in patients with impaired hepatic function.	

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?	Encorafenib (marketed under the name "BRAFTOVI®") has shown efficacy in several BRAF V600 mutant solid cancers; specifically, the combination of encorafenib and binimetinib (marketed under the name "MEKTOVI®") is effective and well tolerated in patients with advanced melanoma whose tumor harbor the BRAF V600 mutation. The liver plays an important part in the way encorafenib is absorbed and then eliminated from the body. Previous clinical trials suggest that elimination is slower for patients having liver dysfunctions (also called HI, for Hepatic Impairment). Following daily administrations, this leads to higher treatment concentration in the body. According to the severity of HI, daily doses of encorafenib and binimetinib may need to be adapted. The purpose of this study is to assess the recommended dose in patients presenting moderate or severe HI.
What are the objectives of the trial and how are they evaluated?	The primary objective of this study is to evaluate the pharmacokinetic (PK) of encorafenib following a single dose and repeated oral dose of encorafenib in combination with binimetinib.

	In addition, the trial will allow: • to evaluate the PK of binimetinib taken in combination with encorafenib. • To evaluate the safety of a repeated dose of encorafenib in combination with binimetinib in regard with the number and type of side effects • To compare the PK profiles between impaired (moderate and severe) and normal hepatic functions
How is the trial conducted?	This is an open-label Phase 1 trial with 12 participants. Participants will be assigned to one of the following 3 study groups : - Group I : 4 participants with normal hepatic function - Group II: 4 participants with moderate hepatic impairment - Group III (*): 4 participants with severe impairment (*) Before proceeding with Group III, safety and PK data will be analysed to ensure whether it is safe and feasible. The impact of hepatic impairment on PK will be assessed requiring serial blood samplings on Day 1 (the day of the first treatment administration), and Day 15 (2 weeks after first administration) After completing the 2-weeks HI assessment phase, participants may continue encorafenib and binimetinib treatments as long as it is beneficial for them. That means as long as the disease does not worsen (disease progression) and the treatment is tolerated. After treatment discontinuation, participant will perform an End of Treatment visit, followed by a Safety Follow-Up visit (30 days after last treatment dose). The schema 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: • Adults participants with BRAF V600-mutant solid tumors • Fulfilling hepatic function criteria specific to each trial groups
What are the trial treatments and how are they administered ?	Dosage of Encorafenib and Binimetinib is adapted for each group of participants as following :

Study Treatments	Pharmaceutical Form and Route of Administration	Dose	Frequency
Group I: participants with normal hepatic function			
Encorafenib	6 × 75 mg oral capsule	450 mg	QD*
Binimetinib	3 × 15 mg oral film-coated tablet	45 mg	BID**
Group II: participants with moderate hepatic impairment			
Encorafenib	2 × 75 mg oral capsule	150 mg	QD*
Binimetinib	1 × 15 mg oral film-coated tablet	15 mg	BID**
Group III: participants with severe hepatic impairment			
Encorafenib[a]	1 × 75 mg oral capsule	75 mg	QD*
Binimetinib	1 × 15 mg oral film-coated tablet	15 mg	BID**

[a]Encorafenib Dose for Group III may be adjusted after analysis of PK and safety data of Groups I and II.
(*) QD (Quaque Die) means that treatment is taken once a day
(**) BID (Bis In Die) means that treatment is taken twice a day.

What are the possible benefits	Encorafenib has shown efficacy in several BRAF V600 mutant cancers; specifically, the combination of encorafenib and binimetinib is

and risks in taking part in the trial?	effective and well tolerated in patients with advanced melanoma whose tumor harbor the BRAF V600 mutation. Expected benefits and risks, as well as side effects of encorafenib and binimetinib are well documented. For patients with moderate and severe HI receiving encorafenib and binimetinib daily, there is a risk that the quantity of treatment circulating in the body is higher than the quantity of treatment circulating in the body of patients with normal hepatic function. Therefore, an appropriate dose reduction combined with close and frequent safety monitoring will minimise this risk. The trial may have potential discomforts and constraints for the participants requiring regular visits at hospital, blood sampling and imaging examinations. Encorafenib and binimetinib can cause side effects for which participants are informed by trial doctors at trial entry and are closely monitored for all the duration of the trial.

Cinical Trial identification

Protocol Number	W00090GE101
Protocol Version	3.0 dated 16 December 2021
Full trial title	An open label, multicentre, phase I study to evaluate the impact of moderate and severe hepatic impairments on the pharmacokinetics and safety of encorafenib in combination with binimetinib in adult patients with unresectable or metastatic BRAF V600-mutant solid tumors.
Registry ID	ClinicalTrials.gov: NCT04759846 EudraCT Number: 2020-000861-17

Who sponsors this trial?

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

Additional Information

Encorafenib (Braftovi®): Summary of product characteristics

Glossary	
Unresectable	that cannot be removed by surgery
BRAF^{V600E}	All humans have a gene called *BRA*F. The *BRAF* gene makes a protein that helps control cell growth. In some patients with colorectal cancer, this gene mutates (V600E mutation) and makes the tumor grow faster.
Metastatic	Metastasic means that cancer has spread to a different part of the body than where it started
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.
Pharmacokinetic	The pharmacokinetic of a drug is how the body absorbs, transforms, and eliminates this drug.
Phase I trials	Phase I trials test an experimental drug, in a small group of people to evaluate safety, identify side effects and determine safe dosages.
Open-label	A type of trial in which both the doctors and the participants are aware of the treatment being given.