Clinical Study Results

This summary reports the results of only one study. Researchers must look at the results of many types of studies to understand if a study medication works, how it works, and if it is safe to prescribe to patients. The results of this study might be different than the results of other studies that the researchers review.

Sponsor:	Pfizer Inc.
Medicine(s) Studied:	Encorafenib and Binimetinib in combination
Protocol Number:	C4221003 (ARRAY-818-103)
Dates of Study:	02 January 2018 to 11 July 2022 for Part 1 and 29 May 2023 for Part 2
Title of this Study:	Pharmacokinetic Drug-drug Interaction Study of Encorafenib and Binimetinib on Probe Drugs in Patients With BRAF V600-mutant Melanoma or Other Advanced Solid Tumors [An Open-Label Phase 1 Study to Evaluate Drug-Drug Interactions of Agents Co-Administered With Encorafenib and Binimetinib in Patients With *BRAF* V600-mutant Unresectable or Metastatic Melanoma or Other Advanced Solid Tumors]
Date(s) of this Report:	12 July 2023

– Thank You –

If you participated in this study, Pfizer, the Sponsor, would like to thank you for your participation.

This summary will describe the study results. If you have any questions about the study or the results, please contact the doctor or staff at your study site.

Why was this study done?

What is unresectable or metastatic advanced melanoma or solid tumor?

Cancer is a disease in which some of the body's cells grow without control and may spread to other parts of the body. Unresectable means a cancer cannot be completely removed by surgery. Metastatic means a cancer has spread from where it started to a distant part of the body. Both unresectable and metastatic cancers are considered as advanced cancers. Melanoma is a skin cancer from melanocytes (cells that color the skin). Solid tumor is the most common type of cancer which forms abnormal mass that usually does not contain any liquid.

Participants in this study had cancer cells which contained a specific change (mutation) in a gene called BRAF. Having the BRAF V600 mutation may cause the cancer cells to grow and spread.

What is encorafenib and binimetinib?

Encorafenib (en-koe-raf-e-nib) (also known by the brand name Braftovi®) and binimetinib (bin-i-me-ti-nib) (also known by the brand name Mektovi®) are 2 different types of cancer growth blockers. They work by targeting certain proteins that help cancer cells to grow. By blocking these proteins, encorafenib and binimetinib may help to stop or slow down the growth of cancer cells.

Encorafenib and binimetinib are both taken by mouth. In this study, these treatments were given together so the study medication is referred to as "encorafenib + binimetinib combination treatment".

A combination treatment of encorafenib + binimetinib have been approved in several countries including the United States, Japan, Canada, and

European Union for the treatment of patients with unresectable or metastatic melanoma which has a *BRAF* V600 mutation.

What was the purpose of this study?

The main purpose of this study was to measure the effect of encorafenib (in combination with binimetinib) on the amount of several other drugs and the effect of a drug called modafinil on the amount of encorafenib in participants with unresectable advanced/ metastatic melanoma or solid tumor with a *BRAF* V600 mutation. Modafinil is a drug used to treat sleeping disorders.

This study did not test if encorafenib and binimetinib are effective in treating advanced/ metastatic melanoma or solid tumors.

Researchers wanted to know:

- **What effect did encorafenib (in combination with binimetinib) have on the amount of several other drugs in the body?**
- **What effect did modafinil have on the amount of encorafenib in the body?**
- **What medical problems did participants have during the study?**

What happened during the study?

How was the study done?

Participants in this study were enrolled into 1 of the 3 treatment groups. In all 3 treatment groups, different drugs were given together with encorafenib and binimetinib.

Enrolment in Group 1 and 2 occurred around the same time. Participants were assigned to Group 1 and 2 by the study team. Enrolment in Group 3 occurred after Group 2 enrolment was completed.

The study period was divided into 2 parts for each participant. In Part 1, participants received encorafenib and binimetinib together with other drugs as described below. In Part 2, participants only received encorafenib and binimetinib until they discontinued, or the study stopped.

Group 1: Participants in Group 1 received the following drugs on 3 different days in Part 1: Day -7, Day 1, and Day 14, see Figure 1 (Day -7 means 7 days prior to Day 1):

- Losartan as tablet (a drug used to treat high blood pressure)
- Midazolam as oral syrup (a drug used to induce sleep)
- Caffeine as oral liquid
- Omeprazole as capsule (a drug used to treat stomach upset)
- Dextromethorphan as capsule (a drug used to suppress coughs)

Participants in Group 1 also received encorafenib and binimetinib every day for the duration of the study, starting at Day 1:

- Six – 75 mg capsules of encorafenib (total daily dose 450 mg)
- Three – 15 mg tablets in the morning and three – 15 mg tablets in the evening of binimetinib (total daily dose 90 mg)

Group 2: Participants in Group 2 received the following drugs on 3 different days in Part 1: Day -7, Day 1, and Day 14, see Figure 1:

- Rosuvastatin as tablet (a drug used to treat high cholesterol)
- Bupropion as tablet (a drug used to treat depression and smoking addiction)

In addition, participants in Group 2 received encorafenib and binimetinib every day for the duration of the study, starting at Day 1:

- Six – 75 mg capsules of encorafenib (total daily dose 450 mg)
- Three – 15 mg tablets in the morning and three – 15 mg tablets in the evening of binimetinib (total daily dose 90 mg)

Group 3: Participants in Group 3 received encorafenib and binimetinib for the duration of the study, starting at Day 1:

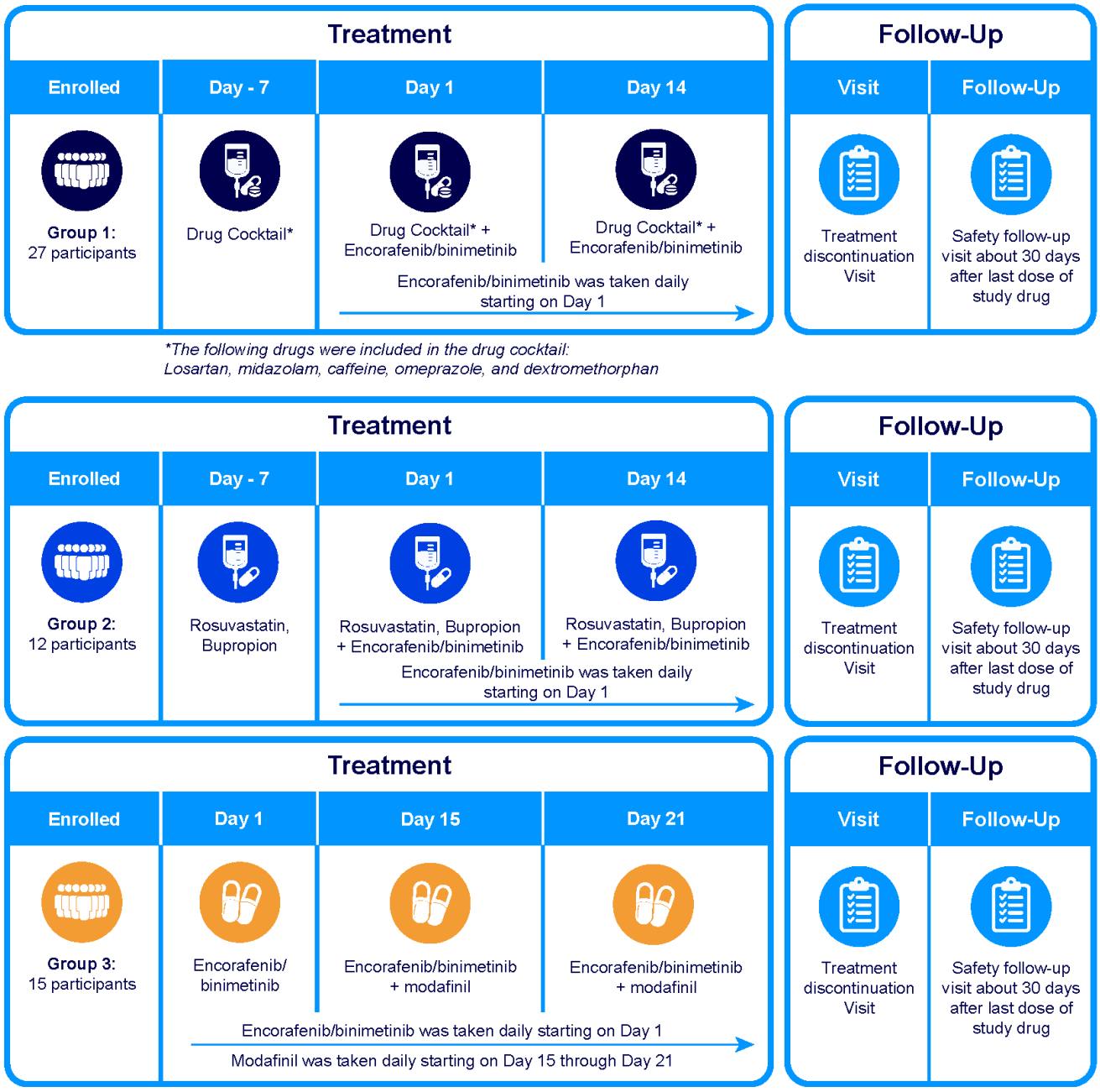
- Six – 75 mg capsules of encorafenib (total daily dose 450 mg)
- Three – 15 mg tablets in the morning and three – 15 mg tablets in the evening of binimetinib (total daily dose 90 mg)

In addition, participants in Group 3 also received modafinil as tablet for 7 consecutive days from Day 15 through Day 21 in Part 1 (see Figure 1):

Researchers took samples of blood and urine from participants during the study and measured the amount of different drugs and their metabolites. Metabolites are chemicals formed as a drug is broken down by the body. Researchers also checked the participants' health during the study and asked them how they were feeling.

This study was an open-label study, which means that participants and doctors knew what study drugs were given to participants. Figure 1 below shows what happened during the study.

Figure 1. Study Design



Where did this study take place?

The Sponsor ran this study at 26 locations in 5 countries in North America and Europe.

When did this study take place?

It began 02 January 2018 and Part 1 of the study ended 11 July 2022. Part 2 of the study ended 29 May 2023, the full report of the results of Part 2 is not yet available. This report summarizes the information collected for Part 1 and Part 2 until August 2020 for Group 2 and July 2022 for Groups 1 and 3.

Who participated in this study?

The study included adult participants who had a confirmed diagnosis of unresectable or metastatic advanced cancer, with a *BRAF* V600 mutation. Participants were required to have received standard treatments for their cancer, but the treatments were not effective or had stopped working, and no additional standard treatments were available.

A total of 56 participants were enrolled in this study: 29 participants in Group 1, 12 participants in Group 2, and 15 participants in Group 3. Of the 29 participants in Group 1, 2 participants discontinued from the study prior to the 1st dose of encorafenib + binimetinib because their cancer got worse and at the discretion of investigator (1 participant each). The following sections summarize the results from the 54 participants who received at least 1 dose of encorafenib and binimetinib.

- A total of 27 men participated
- A total of 27 women participated
- All participants were between the ages of 31 and 82

Of the 27 participants in Group 1, 25 participants completed Part 1 of the study. Two (2) participants stopped taking encorafenib + binimetinib combination treatment in Part 1 and left the study due to medical problems.

All of the 12 participants in Group 2 and all of the 15 participants in Group 3 completed Part 1 of the study.

As of the data collected until July 2022 for Part 2, 15 of the 25 (60.0%) participants in Group 1 stopped taking the study treatment, and 14 participants (56.0%) left before Part 2 of the study was over. The most common reason for participants stopping study treatment was because their cancer got worse (8 participants [32.0%]). The most common reason for participants leaving before Part 2 of the study was completed was also because their cancer got worse (7 participants [28.0%]).

As of the data collected until August 2020, of the 12 participants in Group 2, 7 participants (58.3%) stopped taking the study medication in Part 2 of the study and left before Part 2 of the study was over. The most common reason for stopping study treatment was medical problems (3 participants [25.0%]). The most common reason for leaving before Part 2 of the study was completed was because their cancer got worse (3 participants [25.0%]).

As of the data collected until July 2022, of the 15 participants in Group 3, 14 participants (93.3%) stopped taking the study treatment in Part 2 and left before Part 2 of the study was over. The most common reason for stopping study treatment was because their cancer got worse (12 participants [80.0%]). The most common reason for leaving before Part 2 of the study was over was also because their cancer got worse (9 participants [60.0%]).

How long did the study last?

For Part 1, participants were in the study for 35 days in Groups 1 and 2, and for 28 days in Group 3. The entire Part 1 of the study took 4 years and 6 months to complete. Part 2 of the study took approximately 5 years and 5 months to complete.

Part 1 of the study ended in July 2022 and Part 2 ended in May 2023. The Sponsor reviewed all information collected until July 2022 and created a report of the results. This is a summary of that report.

What were the results of the study?

What was the effect of encorafenib (in combination with binimetinib) on the amount of several other drugs taken by participants in Group 1 and Group 2?

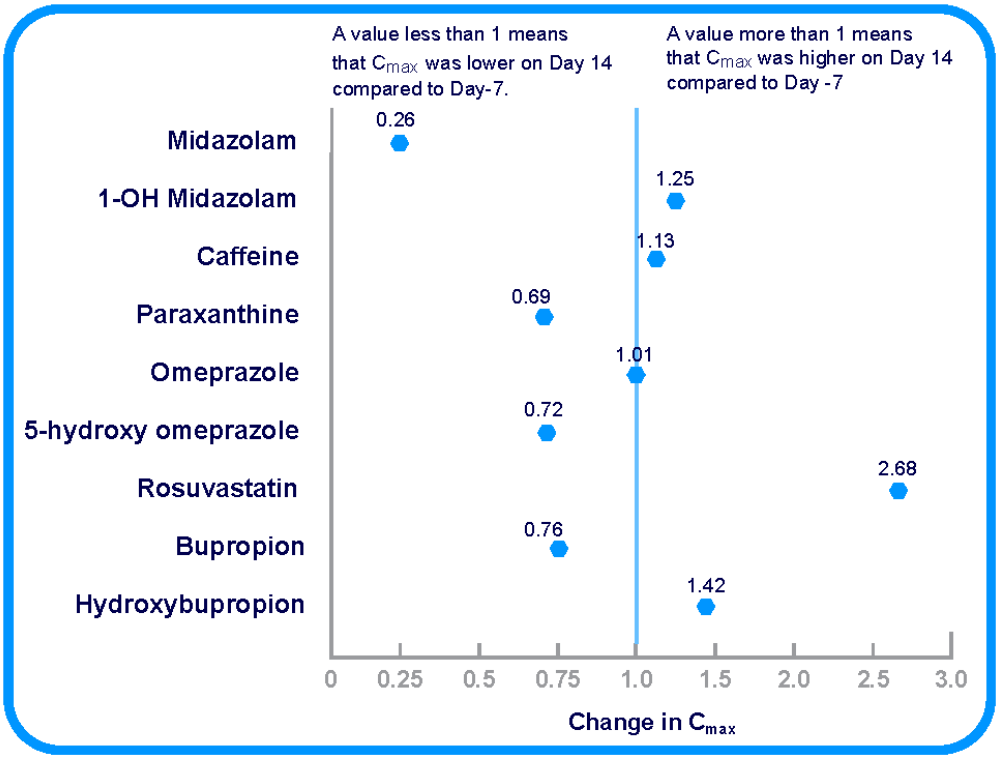
To answer this question, researchers compared blood and urine samples of participants taking different drugs with encorafenib and binimetinib to when they were taking those drugs alone.

What was the amount of different drugs and their metabolites in the blood after participants took those drugs with and without encorafenib and binimetinib?

- The average highest (peak) amount of the drugs and their metabolites in the blood (known as C_{max}) on Day 14 (with encorafenib in combination with binimetinib) compared to Day -7 (without encorafenib and binimetinib) is shown in Figure 2. The blue dot represents the average value of the peak amount of drug in the blood (C_{max}) on Day 14 compared to Day -7. This value is presented next to the blue dot. A value less than 1 means that C_{max}

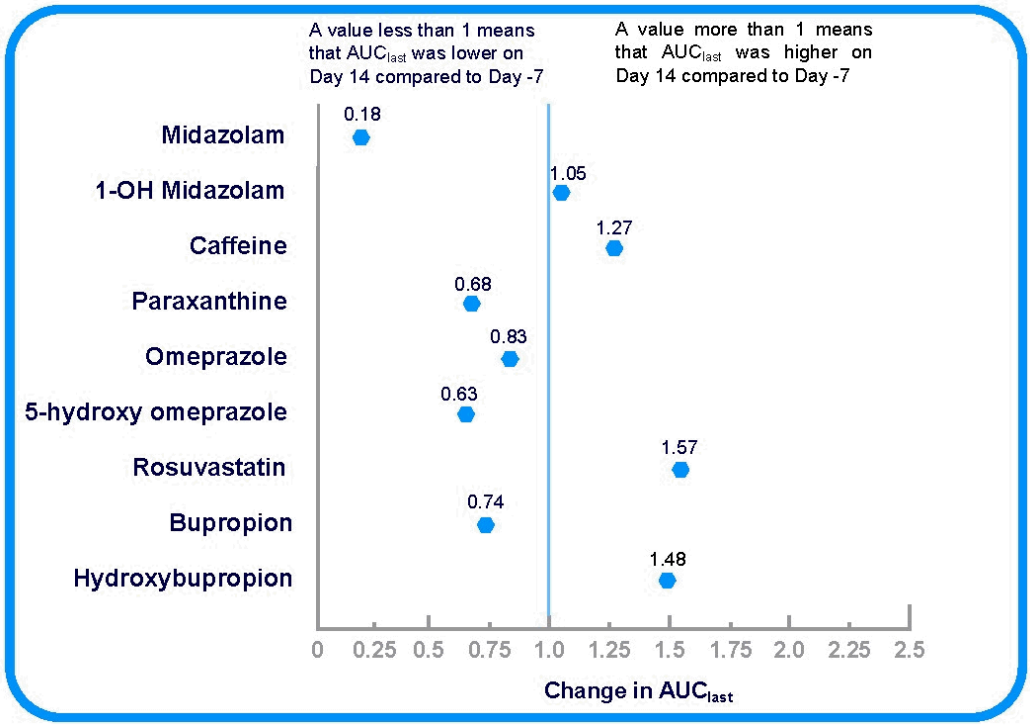
for the drug listed on the left was lower on Day 14 compared to Day -7. A value more than 1 means that C_{max} for the drug listed on the left was higher on Day 14 compared to Day -7.

Figure 2. Effect of Encorafenib in Combination With Binimetinib on the Highest (Peak) Amount of Different Drugs and Their Metabolites in the Blood (C_{max})



- The average total amount of different drugs from when they were taken to the time when the lowest amount was detected in the blood (known as AUC_{last}) on Day 14 (with encorafenib in combination with binimetinib) compared to Day -7 (without encorafenib and binimetinib) is shown in Figure 3.

Figure 3. Effect of Encorafenib in Combination With Binimetinib on the Total Amount of Different Drugs From When They Were Taken to the Time when the Lowest Amount was Detected in the Blood (AUC_{last})



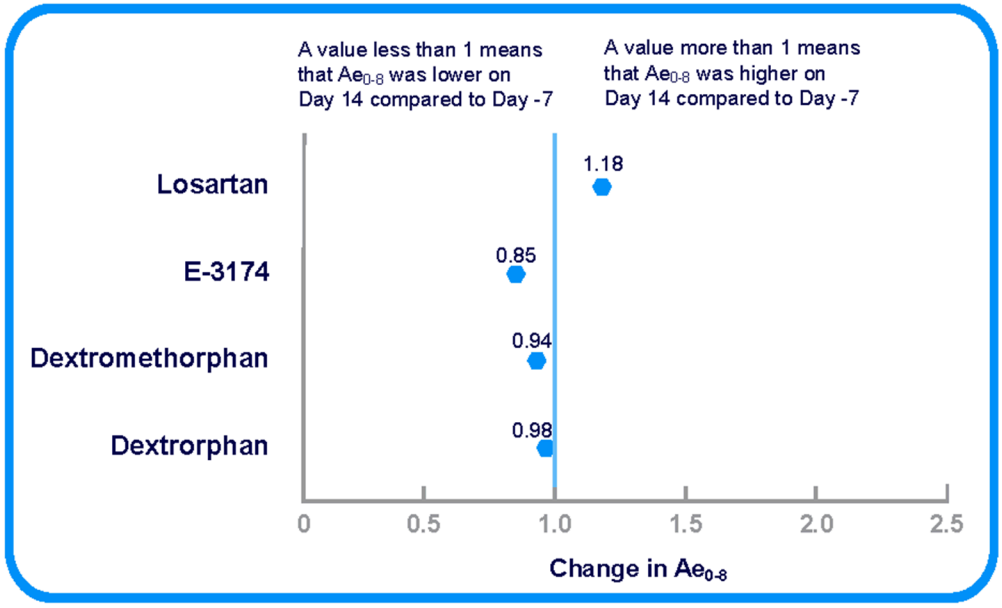
- The following were the results of the highest (peak) amount of drugs in the blood (C_{max}) and total amount of drugs from when they were taken to the time when the lowest amount was detected in the blood (AUC_{last}) from comparison of Day 14 to Day -7
    - When encorefenib (in combination with binimetinib) was taken with midazolam, the C_{max} was decreased by approximately 74%, compared to when midazolam was taken alone. The AUC_{last} of midazolam was decreased by approximately 82% when taken with the combination of encorafenib and binimetinib compared to when it was taken alone.

- The C_{max} and AUC_{last} of caffeine were increased by approximately 13% and 27%, respectively in the presence of encorafenib and binimetinib.
- There was little change in the C_{max} of omeprazole and approximately 17% decrease in the AUC_{last} of omeprazole in the presence of encorafenib and binimetinib.
- There was approximately 2.7-fold increase in the C_{max} and approximately 1.6-fold increase in the AUC_{last} of rosuvastatin in the presence of encorafenib and binimetinib.
- The C_{max} and AUC_{last} of bupropion were decreased by approximately 25% and 26%, respectively in the presence of encorafenib and binimetinib.

What was the amount of drugs and their metabolites that went into the urine over an 8 hour period after participants took those drugs with and without encorafenib in combination with binimetinib?

- Figure 4 shows the amount of drugs that went into the urine over an 8 hour period after participants took those drugs on Day 14 (with encorafenib and binimetinib) compared to Day -7 (without encorafenib and binimetinib). This is known as Ae_{0-8}.
- The blue dot represents the average Ae_{0-8} of different drugs on Day 14 compared to the average Ae_{0-8} on Day -7. This value is presented next to the blue dot. A value less than 1 means that Ae_{0-8} for the drug listed on the left was lower on Day 14 compared to Day -7. A value more than 1 means that Ae_{0-8} for that drug was higher on Day 14 compared to Day -7.

Figure 4. Effect of Encorafenib in Combination With Binimetinib on the Amount of Drugs and Their Metabolites That Went Into the Urine During the 8 Hour Period After Participants Took Those Drugs (Ae_{0-8})



- The amount of losartan that went into the urine during 8 hours after it was taken by the participants was higher when it was taken with encorafenib and binimetinib, compared to when it was taken alone.
- The amount of dextromethorphan that went into the urine during 8 hours after it was taken by the participants was similar when it was taken with encorafenib and binimetinib, compared to when it was taken alone.

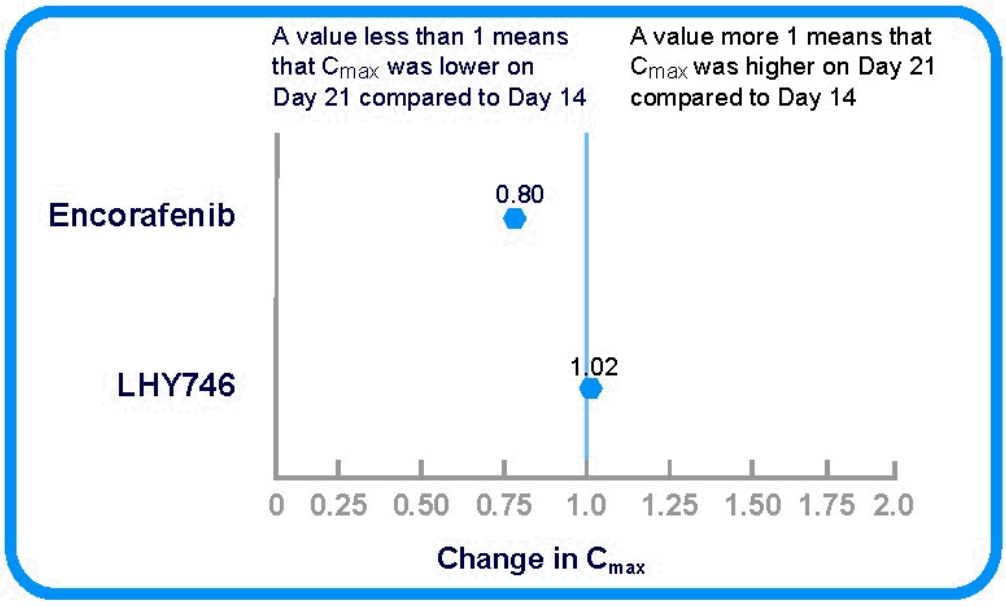
What was the effect of modafinil on the amount of encorafenib?

To answer this question, researchers compared blood samples of participants when they had taken encorafenib and binimetinib with modafinil to when they had taken it without modafinil.

What was the amount of encorafenib and its metabolite in the blood after participants took encorafenib in combination with binimetinib with and without modafinil?

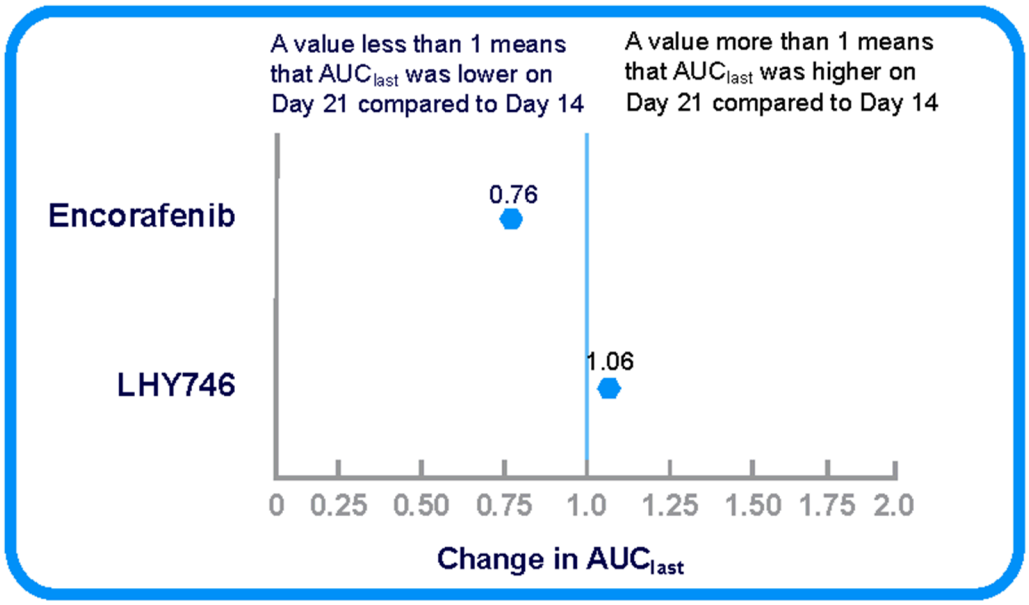
- Figure 5 shows the average highest (peak) amount of encorafenib and its metabolite, LHY746, in the blood (C_{max}) on Day 21 (with modafinil), compared to Day 14 (without modafinil). LHY746 is formed when encorafenib is broken down in the body.
- The blue dot represents the average C_{max} of encorafenib and LHY746 on Day 21 compared to the average C_{max} on Day 14. This value is presented next to the blue dot. A value less than 1 means that C_{max} was lower on Day 21 compared to Day 14. A value more than 1 means that C_{max} was higher on Day 21 compared to Day 14.

Figure 5. Effect of Modafinil on the Highest (Peak) Amount of Encorafenib and its Metabolite, LHY746 in the Blood (C_{max})



- Figure 6 shows the average total amount of encorafenib and its metabolite, LHY746 from when encorafenib was taken to the time when the lowest amount was detected in the blood (AUC_{last}) on Day 21 (with modafinil), compared to Day 14 (without modafinil).

Figure 6. Effect of Modafinil on the Total Amount of Encorafenib and its Metabolite, LHY746 From When Encorafenib was Taken to the Time When the Lowest Amount was Detected in the Blood (AUC_{last})



- For participants in Group 3, there was approximately 20% decrease in the C_{max} and approximately 24% decrease in the AUC_{last} of encorafenib when it was taken with modafinil, compared to when it was taken without modafinil.

Based on these results, the researchers have decided that the results are not likely the result of chance. Some of the drugs examined in this study may act differently in the body when taken with encorafenib in combination with binimetinib. Encorafenib may also act differently in the body when taken with modafinil.

This does not mean that everyone in this study had these results. This is a summary of some of the main results of this study. Other studies may have different results.

What medical problems did participants have during the study?

The researchers recorded any medical problems the participants had during the study. Participants could have had medical problems for reasons not related to the study (for example, caused by an underlying disease or by chance). Or, medical problems could also have been caused by a study treatment or by another medicine the participant was taking. Sometimes the cause of a medical problem is unknown. By comparing medical problems across many treatment groups in many studies, doctors try to understand what effects a study medication might have on a participant.

In Part 1 of the study, a total of 46 participants had at least 1 medical problem, 26 out of 27 participants in Group 1, 9 out of 12 participants in Group 2, and 11 out 15 participants in Group 3. A total of 5 participants left Part 1 of the study because of medical problems, 3 participants in Group 1, and 2 participants in Group 2.

In Part 2 of the study, as of the data collected through July 2022 for Groups 1 and 3, and August 2020 for Group 2, a total of 24 participants had at least 1 medical problem, 16 out of 25 participants in Group 1, 4 out of 12 participants in Group 2, and 4 out 15 participants in Group 3. A total of 6 participants left Part 2 of the study because of medical problems, 4 participants in Group 1, and 2 participants in Group 3.

The most common medical problems – those reported by 3 or more participants in any Group during Part 1 of the study – are described below.

Below are instructions on how to read Table 1.

Instructions for Understanding Table 1.

- The **1st** column of Table 1 lists medical problems that were commonly reported during Part 1 of the study. All medical problems reported by 3 or more participants are listed.
- The **2nd** column tells how many of the 27 participants in Group 1 taking the study medication reported each medical problem during Part 1 of the study. Next to this number is the percentage of the 27 participants in Group 1 taking the study medication who reported the medical problem.
- The **3rd** column tells how many of the 12 participants in Group 2 taking the study medication reported each medical problem during Part 1 of the study. Next to this number is the percentage of the 12 participants in Group 2 taking the study medication who reported the medical problem.
- The **4th** column tells how many of the 15 participants in Group 3 taking the study medication reported each medical problem during Part 1 of the study. Next to this number is the percentage of the 15 participants in Group 3 taking the study medication who reported the medical problem.
- Using these instructions, you can see that:
  - In Group 1, 10 out of the 27 (37.0%) participants taking the study medication reported nausea during Part 1 of the study.
  - In Group 2, 5 out of the 12 (41.7%) participants taking the study medication reported nausea during Part 1 of the study.
  - In Group 3, 4 out of the 15 (26.7%) participants taking the study medication reported nausea during Part 1 of the study.

Table 1. Commonly reported medical problems by study participants during Part 1 of the study

Medical Problem	Group 1 (27 Participants)	Group 2 (12 Participants)	Group 3 (15 Participants)
Nausea	10 out of 27 participants (37.0%)	5 out of 12 participants (41.7%)	4 out of 15 participants (26.7%)
Diarrhoea	8 out of 27 participants (29.6%)	3 out of 12 participants (25.0%)	4 out of 15 participants (26.7%)
Vomiting	7 out of 27 participants (25.9%)	2 out of 12 participants (16.7%)	1 out of 15 participants (6.7%)
Feeling Tired	5 out of 27 participants (18.5%)	3 out of 12 participants (25.0%)	2 out of 15 participants (13.3%)
Blurred vision	6 out of 27 participants (22.2%)	0 out of 12 participants (0%)	2 out of 15 participants (13.3%)
Headache	3 out of 27 participants (11.1%)	2 out of 12 participants (16.7%)	3 out of 15 participants (20.0%)
Decreased appetite	3 out of 27 participants (11.1%)	2 out of 12 participants (16.7%)	2 out of 15 participants (13.3%)
Constipation	5 out of 27 participants (18.5%)	1 out of 12 participants (8.3%)	0 out of 15 participants (0%)
Fever	4 out of 27 participants (14.8%)	2 out of 12 participants (16.7%)	0 out of 15 participants (0%)

Table 1. Commonly reported medical problems by study participants during Part 1 of the study

Medical Problem	Group 1 (27 Participants)	Group 2 (12 Participants)	Group 3 (15 Participants)
Lipase increased (lipase helps your body digest fats)	6 out of 27 participants (22.2%)	0 out of 12 participants (0%)	0 out of 15 participants (0%)
Dizziness	3 out of 27 participants (11.1%)	1 out of 12 participants (8.3%)	1 out of 15 participants (6.7%)
Increased muscle protein (creatinine phosphokinase) in blood	3 out of 27 participants (11.1%)	1 out of 12 participants (8.3%)	1 out of 15 participants (6.7%)
Low red blood cell count	0 out of 27 participants (0%)	4 out of 12 participants (33.3%)	1 out of 15 participants (6.7%)
Increased creatinine levels (sign of kidney problems)	3 out of 27 participants (11.1%)	0 out of 12 participants (0%)	1 out of 15 participants (6.7%)
Loss of strength or energy	0 out of 27 participants (0%)	1 out of 12 participants (8.3%)	3 out of 15 participants (20.0%)

Table 1. Commonly reported medical problems by study participants during Part 1 of the study			
Medical Problem	**Group 1 (27 Participants)**	**Group 2 (12 Participants)**	**Group 3 (15 Participants)**
Amylase increased (amylase helps your body digest carbohydrates)	3 out of 27 participants (11.1%)	0 out of 12 participants (0%)	0 out of 15 participants (0%)

Did study participants have any serious medical problems?

A medical problem is considered “serious” when it is life-threatening, needs hospital care, or causes lasting problems.

A total of 3 participants had serious medical problems during Part 1 of the study.

Two (2) of the 27 participants (7.4%) in Group 1 had serious medical problems. Of these, researchers believed 1 participant (3.7%) had serious medical problems that were related to at least 1 of the study treatments. Serious medical problems related to study treatments were nausea, vomiting, chills and fever.

In Group 2, 1 of the 12 participants (8.3%) had serious medical problem (fever), which the researchers believed to be related to the study treatment.

None of the participants in Group 3 had serious medical problems during Part 1 of the study.

During Part 2 of the study, as of the data collected through July 2022 for Group 1, 11 of the 25 participants (44.0%) had serious medical problems, of which 3 participants (12.0%) had serious medical problems that were related to at least 1 of the study treatments. Serious medical problems related to study treatments were fever, flu-like illness, increased liver enzyme (transaminase), and dehydration.

For Group 2, as of the data collected until August 2020, 2 of 12 participants (16.7%) had serious medical problems during Part 2 of the study, none of them were considered to be related to the study treatment.

For Group 3, as of the data collected until July 2022, 3 of the 15 participants (20.0%) had serious medical problems during Part 2 of the study, of which 1 participant had serious medical problem (diarrhoea) that was related to the study treatment.

No participants in any Group died during Part 1 of the study.

In Part 2 of the study, as of the data collected through July 2022 for Groups 1 and 3, and August 2020 for Group 2, a total of 4 participants died. One (1) participant died in Group 1 due to bleeding in the brain. The researchers believed that this was due to their cancer getting worse and not related to the study treatment. Three (3) participants died in Group 3 due to their cancer getting worse.

Where can I learn more about this study?

If you have questions about the results of your study, please speak with the doctor or staff at your study site.

For more details on your study protocol, please visit:

www.pfizer.com/research/research_clinical_trials/trial_results	Use the protocol number **C4221003**

The full scientific report of this study is available online at:

www.clinicaltrials.gov	Use the study identifier **NCT03864042**
www.clinicaltrialsregister.eu	Use the study identifier **2019-001036-66**

Please remember that researchers look at the results of many studies to find out which medicines can work and are safe for patients.

Again, if you participated in this study, **thank you** for volunteering. We do research to try to find the best ways to help patients, and you helped us to do that!