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 (eMCC and eMCCL) + Rabeprazole (PF-07263896)
Protocol Number:	C4221024
Dates of Study:	01 July 2022 to 30 September 2022
Title of this Study:	A study of two new encorafenib formulations and the effect of a proton-pump inhibitor on these formulations in adult healthy participants [A Phase 1, Randomized, Open-Label Study in Healthy Participants to Estimate the Bioavailability of Two New Encorafenib Formulations Relative to the Current Formulation and to Evaluate the Effect of a Proton-Pump Inhibitor on Encorafenib Plasma Pharmacokinetics]
Date(s) of this Report:	19 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 metastatic melanoma?

Cancer is the name for a group of diseases in which abnormal cells divide without control. Metastatic melanoma is a form of cancer that starts in the skin and spreads to other areas of the body. Unresectable cancer is a cancer that cannot be completely removed by surgery.

What is encorafenib?

Encorafenib is a cancer growth blocker. It targets cancer cells which contain a specific change (mutation) in a gene called BRAF. Having the BRAF V600 mutation may cause the cancer cells to grow and spread. By blocking these proteins, encorafenib treatment may help to stop or slow down the growth of cancer cells. Encorafenib was given orally to the healthy participants.

What was the purpose of this study?

The purpose of this study was to learn how the 2 new encorafenib formulations (eMCC [immediate-release tablet formulated with MCC] and eMCCL [immediate-release tablet formulated with MCC and lactose]) compare to how the commercially available formulation (CAP [encorafenib formulated capsule]) move through the body. Also, to learn how long the eMCC and eMCCL formulations stay in the body after being given with rabeprazole (proton pump inhibitor [PPI] used to reduce stomach acid).

After encorafenib was swallowed, encorafenib entered the body and moved through the body. Encorafenib entered the blood and organs (for example, stomach, liver, and kidneys) when it moved through the body. Afterwards, encorafenib was removed from the body through urine and feces.

This study did not test if the 2 new encorafenib formulations helps to treat metastatic melanoma.

This study was conducted to learn more about the differences between 2 new encorafenib formulations. The results were based on the amount of drug in the body after a single dose, given under fasting conditions.

Researchers wanted to know:

- **How did the 2 new encorafenib formulations act in the body when compared to the commercially available formulation given under fasting conditions (without food)?**
- **How did the 2 new encorafenib formulations act in the body in the presence of rabeprazole?**
- **What medical problems participants had during the study**

What happened during the study?

How was the study done?

Researchers tested 4 single 75 mg doses of encorafenib and one 20 mg dose of rabeprazole on a group of healthy participants to learn how encorafenib acted in the body.

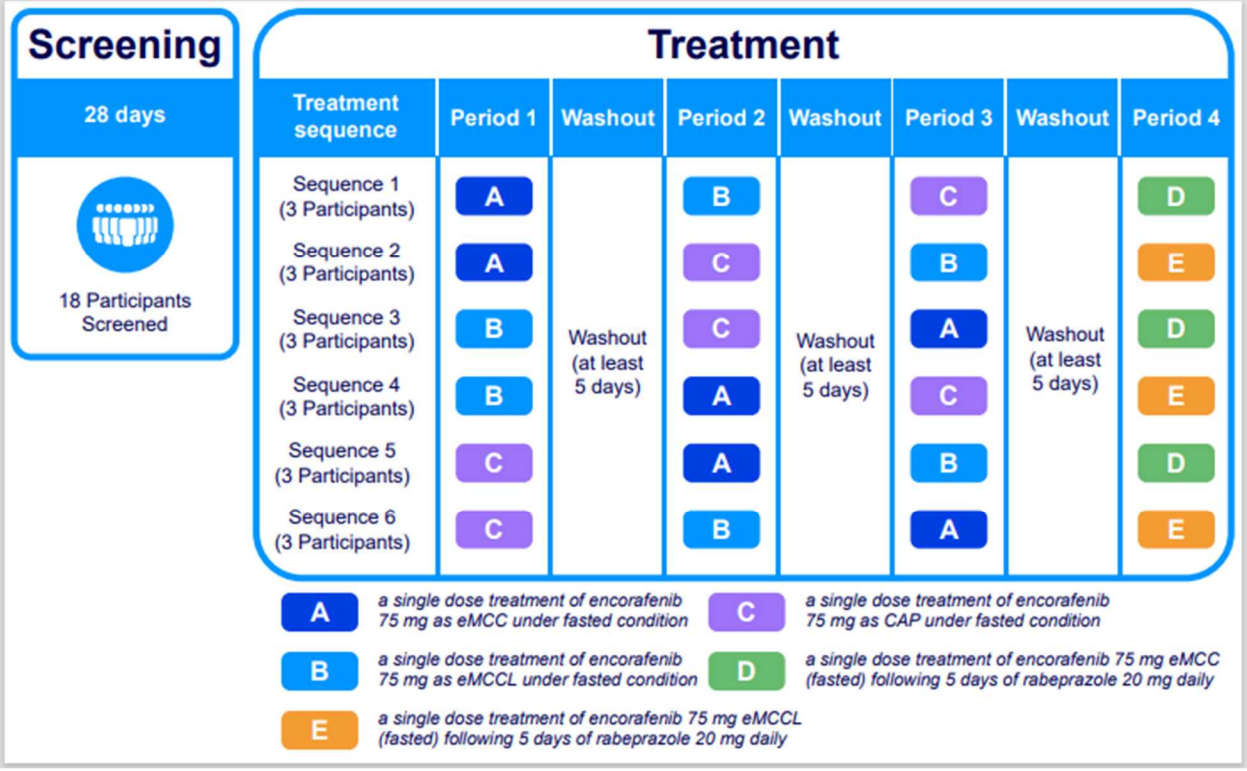
Participants in this study were enrolled into 1 of the 6 treatment sequence (4-period, 6-sequence). A total of 5 treatment options (Treatments A to E) were planned as follows:

- Treatment A: a single dose of encorafenib 75 mg as eMCC under fasted condition

- Treatment B: a single dose of encorafenib 75 mg as eMCCL under fasted condition
- Treatment C: a single dose of encorafenib 75 mg as CAP under fasted condition
- Treatment D: a single dose of encorafenib 75 mg eMCC (fasted) following 5 days of rabeprazole 20 mg daily
- Treatment E: a single dose of encorafenib 75 mg eMCCL (fasted) following 5 days of rabeprazole 20 mg daily

For Periods 1 through 3, participants received a single 75 mg encorafenib formulation on Day 1 of each period: eMCC (Treatment A), eMCCL (Treatment B), and CAP (Treatment C), all under fasted conditions. A minimum 5-day 'washout period' (no treatment given to participants on those days to allow time for a drug to be removed from the body) between encorafenib doses was exercised in these periods. Periods 1 through 3 were intended to estimate the amount of the 2 new encorafenib immediate release tablet formulations that entered the blood when compared to the commercially available CAP formulation.

For Period 4, participants received either a single 75 mg dose of eMCC (Treatment D) or eMCCL (Treatment E) after 5 days of 20 mg once daily rabeprazole. Period 4 was intended to explore the potential effect of rabeprazole on how the encorafenib eMCC and eMCCL formulations entered and moved through the body and how long it stayed in the body of participants receiving one of the formulations with rabeprazole.



Researchers took samples of blood from participants during the study and measured the amount of encorafenib in the plasma. Researchers also checked the participants' health during the study and asked them how they were feeling.

Researchers then compared the results of participants taking the 2 new immediate release formulations of encorafenib (eMCC and eMCCL) to the CAP formulation. They also observed whether the rabeprazole changed the amount of eMCC or eMCCL encorafenib formulations in the body when they were given together.

Participants were assigned to each group by chance alone. This study was an "open-label" study, which means that participants and researchers knew which medicines the participants received.

Where did this study take place?

The Sponsor ran this study at 1 location in the United States.

When did this study take place?

It began 01 July 2022 and ended 30 September 2022.

Who participated in this study?

The study included healthy participants who were 18 years of age or older.

- A total of 13 men participated
- A total of 5 women participated
- All participants were between the ages of 24 and 78 years

Of the 18 participants who started the study, 18 (100.0%), 17 (94.4%), 17 (100.0%), 8 (100.0%), and 9 (100.0%) finished Treatment sequence A, B, C, D, and E of the study, respectively. One (1) participant (5.6%) did not finish the study because of an adverse event.

One (1) participant left before the study was over by their choice or a doctor decided it was best for a participant to stop being in the study. This participant stopped participating in the study because of a medical problem which was not related to the study treatment.

How long did the study last?

Study participants were in the study for 7 weeks. The entire study took approximately 12 weeks to complete.

When the study ended in September 2022, the Sponsor began reviewing the information collected. The Sponsor then created a report of the results. This is a summary of that report.

What were the results of the study?

How did the 2 new immediate release formulations of encorafenib (eMCC and eMCCL) act in the body when compared to the CAP formulation and when they were given in combination with rabeprazole?

To answer this question, researchers compared blood plasma samples of participants taking 2 new immediate release formulations of encorafenib (eMCC and eMCCL) to the CAP formulation in the first part of the study.

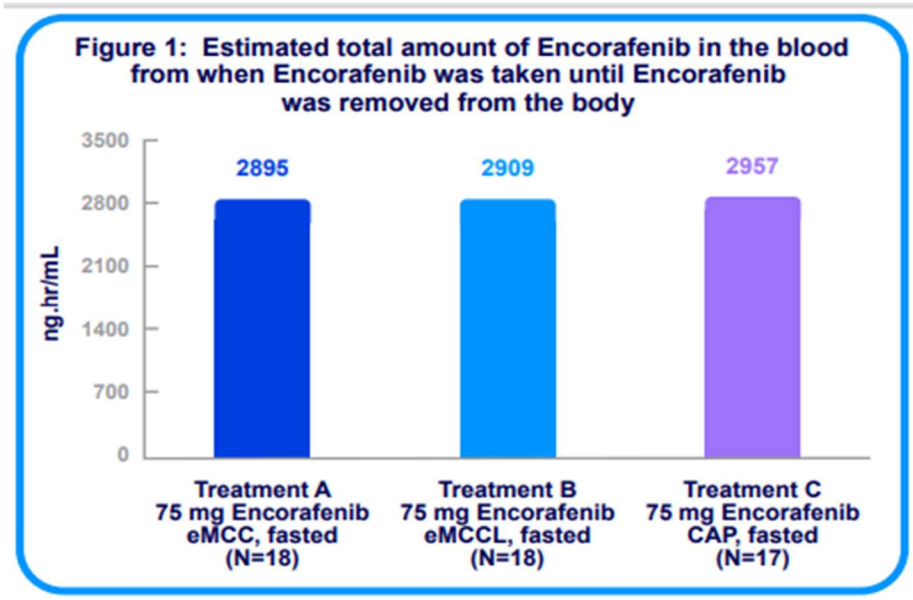
After this, the eMCC and eMCCL formulations were also given together with rabeprazole. The blood plasma samples were compared to when participants in the study had taken the eMCC and eMCCL formulations alone.

What was the total amount of Encorafenib in the blood from when it was taken until it was removed from the body after participants took 75 mg of encorafenib?

- The estimated total amount of Encorafenib in the blood from when it was taken until it was removed from the body (AUC_{inf}) after participants took 75 mg of encorafenib is shown in Figure 1, Figure 2, and Figure 3. The amount of drug in the blood was measured in nanogram hours per milliliter, also called ng•hr/mL. The ng•hr/mL is a unit used to measure the total amount of drug over time in the blood.

- In this study, the AUC_{inf} for Treatment A and B were similar to the Treatment C (CAP).

- The AUC_{inf} for Treatment E and D were similar compared to Treatments A (eMCC formulation alone) and B (eMCCL formulation alone), respectively.



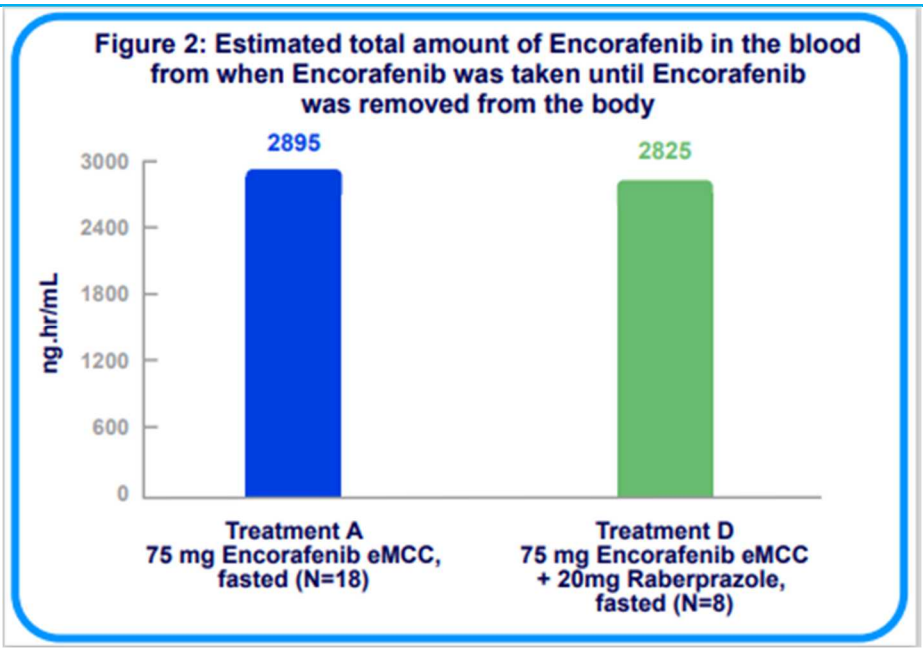


Figure 2: Estimated total amount of Encorafenib in the blood from when Encorafenib was taken until Encorafenib was removed from the body
2895
2825
3000
2400
1800
1200
600
0
ng.hr/mL
Treatment A
75 mg Encorafenib eMCC, fasted (N=18)
Treatment D
75 mg Encorafenib eMCC + 20mg Raberprazole, fasted (N=8)

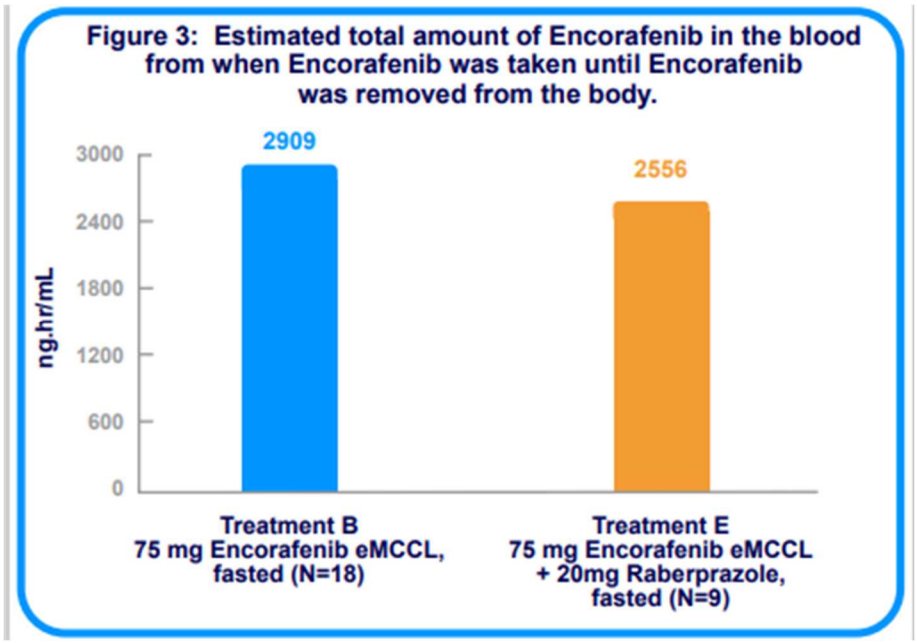
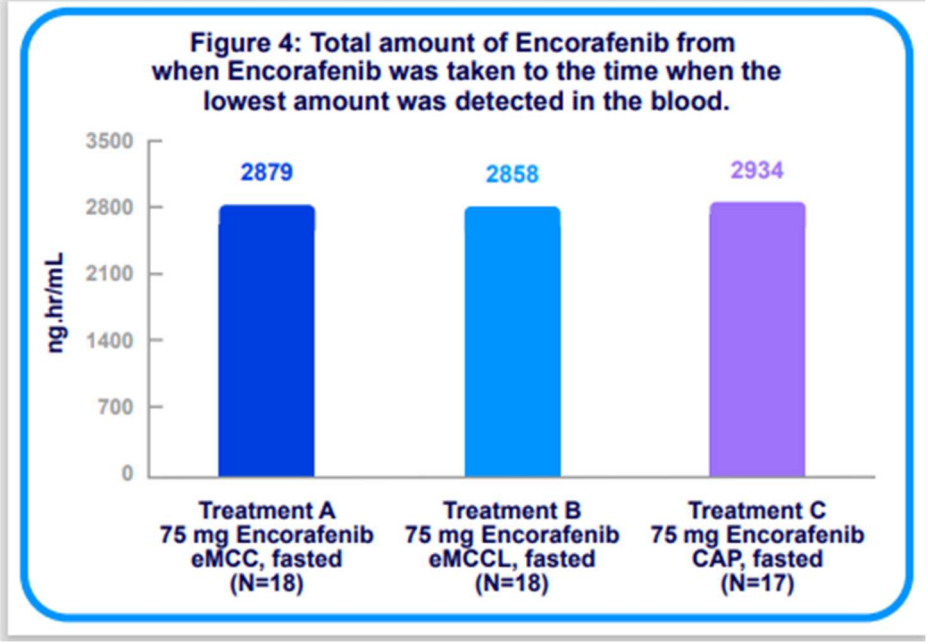


Figure 3: Estimated total amount of Encorafenib in the blood from when Encorafenib was taken until Encorafenib was removed from the body.
2909
2556
3000
2400
1800
1200
600
0
ng.hr/mL
Treatment B
75 mg Encorafenib eMCCL, fasted (N=18)
Treatment E
75 mg Encorafenib eMCCL + 20mg Raberprazole, fasted (N=9)

What was the total amount of Encorafenib from when it was taken to the time when the lowest amount was detected in the blood?

- The total amount of encorafenib from when it was taken to the time when the lowest amount was detected in the blood (AUC_{last}) after participants took 75 mg of encorafenib was measured in nanogram hours per milliliter, also called ng•hr/mL and is shown in Figure 4, Figure 5, and Figure 6.
- In this study, the AUC_{last} for Treatment A and B were similar to the Treatment C (CAP).
- The AUC_{last} for Treatment E and D were similar compared to Treatments A (eMCC formulation alone) and B (eMCCL formulation alone), respectively.



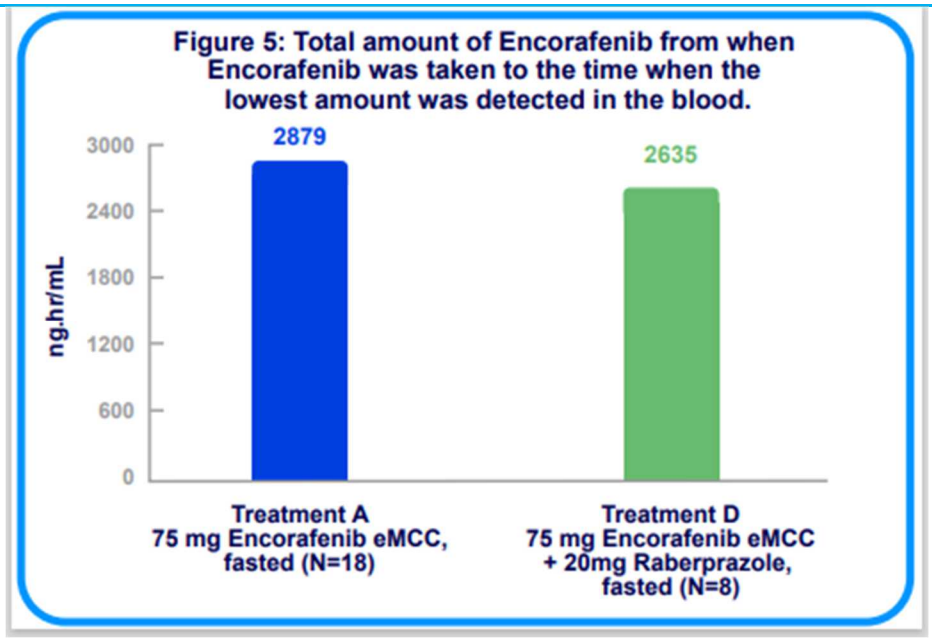


Figure 5: Total amount of Encorafenib from when Encorafenib was taken to the time when the lowest amount was detected in the blood.
2879
2635
3000
2400
1800
1200
600
0
ng.hr/mL
Treatment A
75 mg Encorafenib eMCC, fasted (N=18)
Treatment D
75 mg Encorafenib eMCC + 20mg Raberprazole, fasted (N=8)

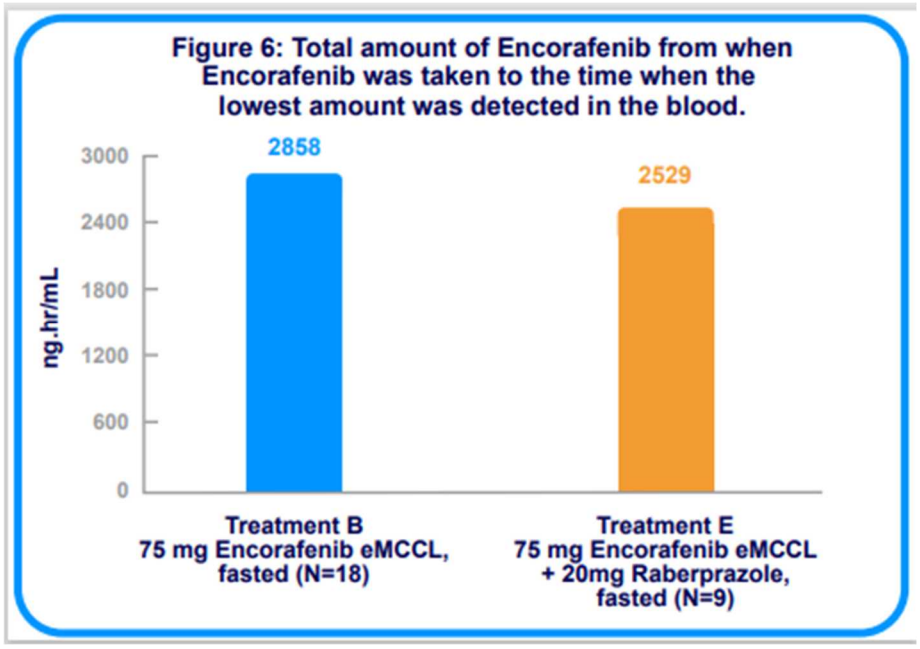
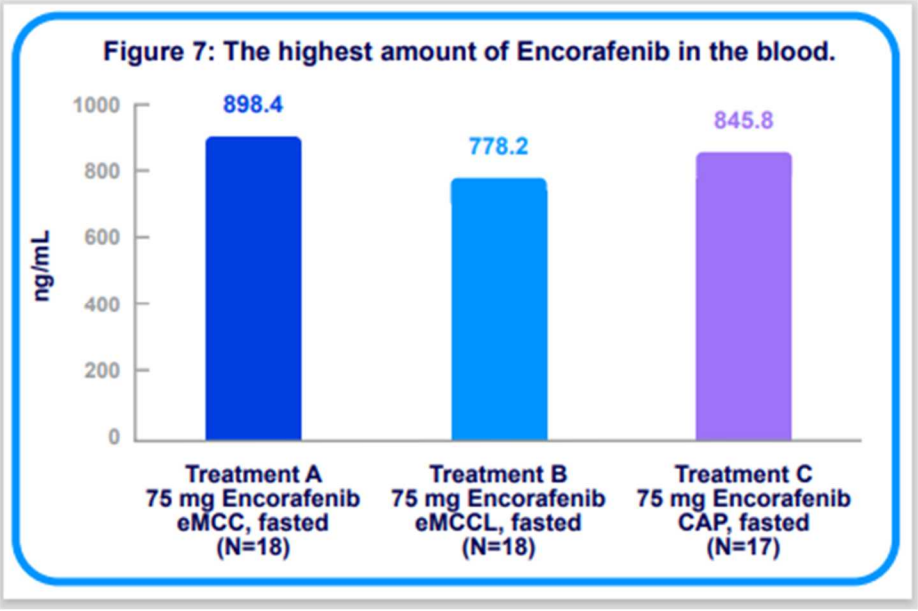
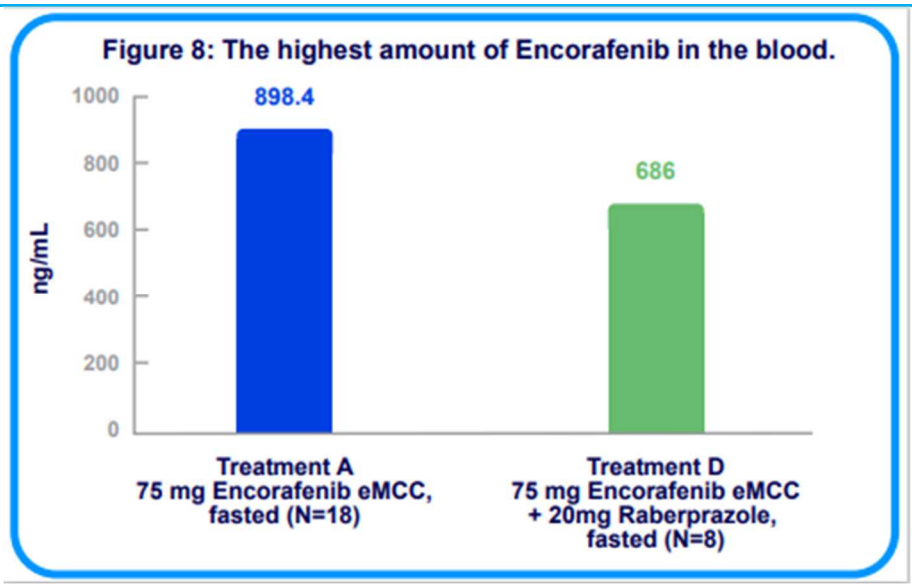


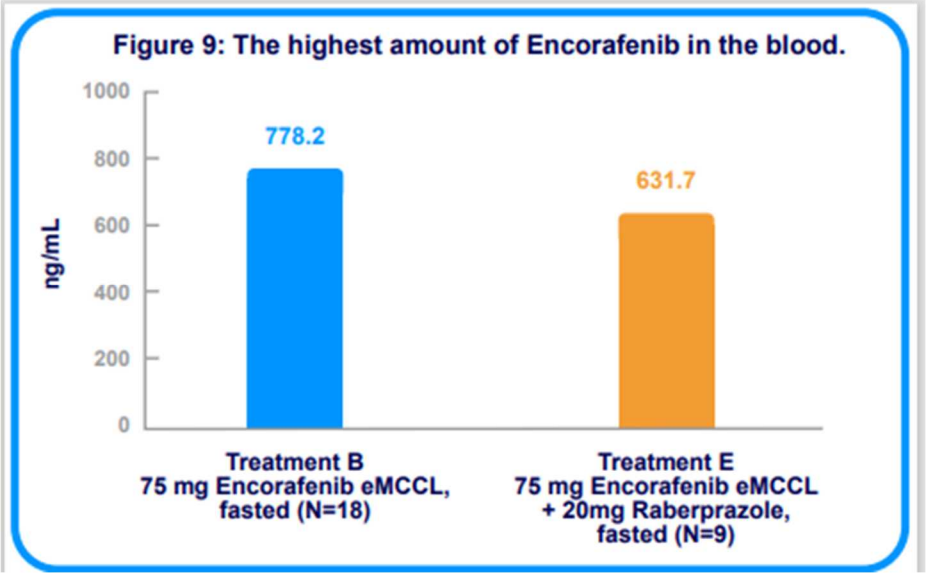
Figure 6: Total amount of Encorafenib from when Encorafenib was taken to the time when the lowest amount was detected in the blood.
2858
2529
3000
2400
1800
1200
600
0
ng.hr/mL
Treatment B
75 mg Encorafenib eMCCL, fasted (N=18)
Treatment E
75 mg Encorafenib eMCCL + 20mg Raberprazole, fasted (N=9)

What was the highest amount of Encorafenib detected in the blood after participants took 75 mg of Encorafenib?

- The highest amount of Encorafenib detected in the blood (C_{max}) after participants took 75 mg of Encorafenib is shown in Figure 7. The amount of drug in the blood was measured in nanograms per milliliter, also called ng/mL.
- The C_{max} for Treatment A was similar to the Treatment C (CAP). Researchers considered the difference in the results as minor.
- The C_{max} for Treatment D and E were similar compared to Treatments A (eMCC formulation alone) and B (eMCCL formulation alone), respectively and shown in Figure 8 and Figure 9.







- Overall, the intensity of the PPI effect on encorafenib movement through the body was lower with the eMCC formulation (Treatment D) compared to that observed with the eMCCL formulation (Treatment E) in the presence of rabeprazole.

Based on these results, the researchers have decided that the results are not likely the result of chance. The study medication may act differently in the body than in the presence of rabeprazole.

This does not mean that everyone in this study had these results. This is a summary of just 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.

11 out of 18 [61.1]% participants in Treatment group A and B, 8 out of 17 [47.1]% participants in Treatment group C, 1 out of 8 [12.5]% participants in Treatment group D, and 5 out of 9 [55.6]% participants in Treatment group E in this study had at least 1 medical problem. A total of 1 [5.6]% participant left the study because of medical problems. The most common medical problems – those reported by more than 10% of participants – 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 the study. All medical problems reported by more than 10% of participants are listed.
- The **2nd** and **3rd** column tells how many of the 18 participants taking the study medication (Treatment A and B) reported each medical problem. Next to this number is the percentage of the 18 participants taking the study medication who reported the medical problem.
- The **4th** column tells how many of the 17 participants taking another medicine (comparator Treatment C) reported each medical problem. Next to this number is the percentage of the 17 participants taking another medicine (comparator) who reported the medical problem.
- The **5th** and **6th** column tells how many of the 8 and 9 participants respectively, taking study medication (Treatment D and E) along with proton pump inhibitor reported each medical problem. Next to this number is the percentage of the participants taking study medication along with proton pump inhibitor who reported the medical problem.
- Using these instructions, you can see that 5 out of the 17 [29.4]% participants taking the comparator (Treatment C) reported headache.

Table 1. Commonly reported medical problems by study participants					
Medical Problem	Treatment A (18 Participants)	Treatment B (18 Participants)	Treatment C (17 Participants	Treatment D (8 Participants	Treatment E (9 Participants
Feeling hot	4 out of 18 participants (22.2%)	4 out of 18 participants (22.2%)	1 out of 17 participants (5.9%)	0 out of 8 participants (0.0%)	0 out of 9 participants (0.0%)
Headache	4 out of 18 participants (22.2%)	2 out of 18 participants (11.1%)	5 out of 17 participants (29.4%)	1 out of 8 participants (12.5%)	2 out of 9 participants (22.2%)
Chills	1 out of 18 participants (5.6%)	0 out of 18 participants (0.0%)	0 out of 17 participants (0.0%)	0 out of 8 participants (0.0%)	1 out of 9 participants (11.1%)
Light-headedness (dizziness)	1 out of 18 participants (5.6%)	0 out of 18 participants (0.0%)	0 out of 17 participants (0.0%)	0 out of 8 participants (0.0%)	1 out of 9 participants (11.1%)
Burning, tingling sensation, or numbness on the lips, tongue, or entire mouth (paraesthesia oral)	1 out of 18 participants (5.6%)	1 out of 18 participants (5.6%)	0 out of 17 participants (0.0%)	0 out of 8 participants (0.0%)	1 out of 9 participants (11.1%)
Reduced desire to eat is (decreased appetite)	0 out of 18 participants (0.0%)	0 out of 18 participants (0.0%)	0 out of 17 participants (0.0%)	0 out of 8 participants (0.0%)	1 out of 9 participants (11.1%)

Nerve pain (dysaesthesia)	0 out of 18 participants (0.0%)	2 out of 18 participants (11.1%)	1 out of 17 participants (5.9%)	0 out of 8 participants (0.0%)	1 out of 9 participants (11.1%)
Indigestion (dyspepsia)	0 out of 18 participants (0.0%)	0 out of 18 participants (0.0%)	0 out of 17 participants (0.0%)	1 out of 8 participants (12.5%)	0 out of 9 participants (0.0%)
Pain in any part of the face (facial pain)	0 out of 18 participants (0.0%)	0 out of 18 participants (0.0%)	0 out of 17 participants (0.0%)	0 out of 8 participants (0.0%)	1 out of 9 participants (11.1%)
Feeling tired (fatigue)	0 out of 18 participants (0.0%)	2 out of 18 participants (11.1%)	0 out of 17 participants (0.0%)	0 out of 8 participants (0.0%)	0 out of 9 participants (0.0%)
Skin blushing or sudden reddening due to increased blood flow (flushing)	0 out of 18 participants (0.0%)	2 out of 18 participants (11.1%)	0 out of 17 participants (0.0%)	0 out of 8 participants (0.0%)	0 out of 9 participants (0.0%)
Sudden feeling of warmth in the upper body (hot flush)	0 out of 18 participants (0.0%)	1 out of 18 participants (5.6%)	2 out of 17 participants (11.8%)	0 out of 8 participants (0.0%)	0 out of 9 participants (0.0%)
Abnormal sensation of the body, such as numbness, tingling, or burning (paraesthesia)	0 out of 18 participants (0.0%)	2 out of 18 participants (11.1%)	0 out of 17 participants (0.0%)	0 out of 8 participants (0.0%)	1 out of 9 participants (11.1%)

Ingrowing hairs in the beard area (pseudofolliculitis)	0 out of 18 participants (0.0%)	0 out of 18 participants (0.0%)	0 out of 17 participants (0.0%)	0 out of 8 participants (0.0%)	1 out of 9 participants (11.1%)

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.

No participants had serious medical problems.

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 C4221024

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

www.clinicaltrials.gov	Use the study identifier **NCT05446142**

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!