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Daiichi-Sankyo

Impact of Meal Contents and Intake Timing on Pexidartinib Exposure

March 2023

US Medical Affairs

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- Pexidartinib is approved for use in the US, South Korea, and Taiwan for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery. Its use is investigational in all other countries.

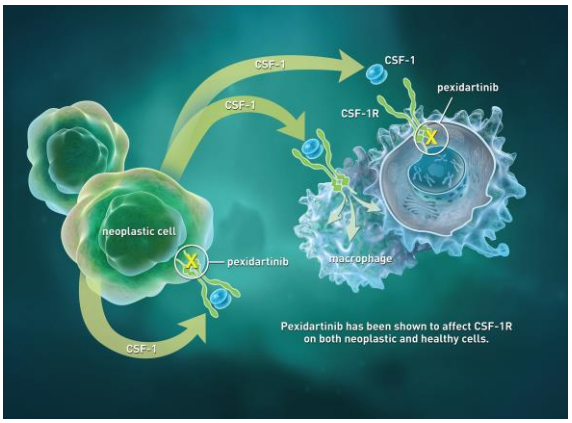
Pexidartinib Inhibits Colony Stimulating Factor-1 Receptor (CSF-1R)

Pathophysiology of TGCT

- Overexpression of the CSF-1R ligand promotes cell proliferation and accumulation in the synovium

Pexidartinib Mechanism of Action

- Pexidartinib is a small molecule tyrosine kinase inhibitor that targets CSF-1R, KIT proto-oncogene receptor tyrosine kinase (KIT), and FMS-like tyrosine kinase 3 (FLT3) harboring an internal tandem duplication (ITD) mutation
- In vitro, pexidartinib inhibited proliferation of cell lines dependent on CSF-1R and ligand-induced autophosphorylation of CSF-1R
- Pexidartinib also inhibited the proliferation of a CSF-1R–dependent cell line in vivo



Pexidartinib is currently approved for use in the USA, South Korea, and Taiwan.

Reference: Turalio. Prescribing Information. Daiichi Sankyo, Inc.; 2022.

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Pathophysiology of TGCT

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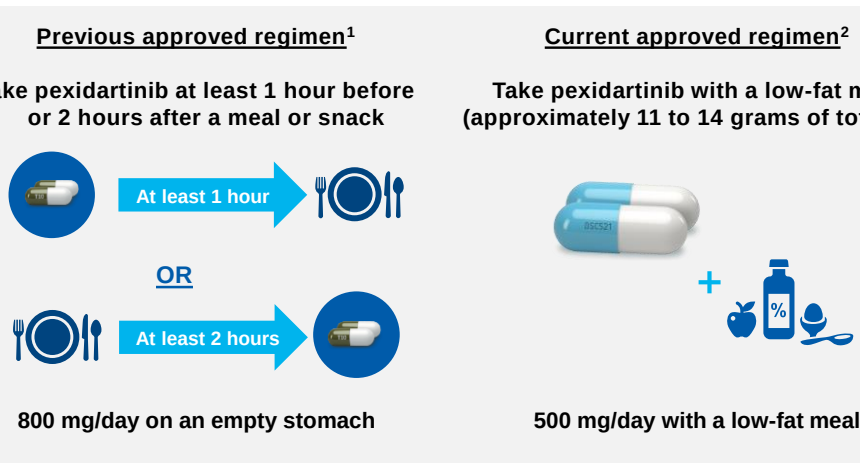
Reference

Turalio. Prescribing Information. Daiichi Sankyo, Inc.; 2022.

As of February 1, 2023, 125 mg Pexidartinib Capsules Are Available and Should Be Taken With a Low-fat Meal



References: 1. Turalio. Prescribing Information. Daiichi Sankyo, Inc.; 2020. 2. Turalio. Prescribing Information. Daiichi Sankyo, Inc.; 2022.

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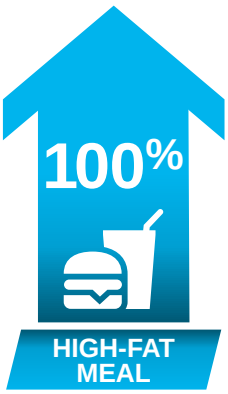
- Pexidartinib is approved for use in the US, South Korea, and Taiwan
- The US prescribing information for pexidartinib at initial approval included instructions to administer pexidartinib on an empty stomach, at least 1 hour before or 2 hours after a meal or snack[1]
- In the October 2022 label update, the recommended dose of pexidartinib was changed from 800 mg/day on an empty stomach to 500 mg/day with a low-fat meal[1,2]

References

1. Turalio. Prescribing Information. Daiichi Sankyo, Inc.; 2020.
2. Turalio. Prescribing Information. Daiichi Sankyo, Inc.; 2022.

Potential Risks Associated With a High-fat Meal



800-1000 KCAL; ~50% OF CALORIES FROM FAT

The solubility of pexidartinib is pH-dependent. A high-fat diet lowers the pH, which makes pexidartinib more soluble, and more of the dose can be absorbed[1]

Administration of pexidartinib with a high-fat meal increases pexidartinib exposure by 100%[2*]

Increased exposure to pexidartinib may increase the incidence and severity of adverse events, including hepatotoxicity[2]

Patients are instructed to avoid taking pexidartinib with a high-fat meal (approximately 55 to 65 grams of total fat)[2]

*Compared with administration of pexidartinib in a fasted state.
References: 1. Daiichi Sankyo, Inc. Data on File. **2.** Turalio. Prescribing Information. Daiichi Sankyo, Inc.; 2022.

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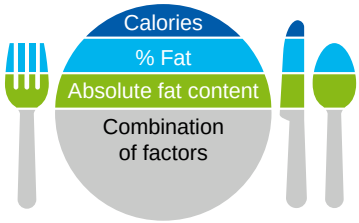
- The solubility of pexidartinib is pH-dependent. A high-fat diet lowers the pH, which makes pexidartinib more soluble, and more of the dose can be absorbed[1]
- Administration of pexidartinib with a high-fat meal increases pexidartinib exposure by 100%, which may increase the incidence and severity of adverse events, including hepatotoxicity[2]
- The US prescribing information for pexidartinib includes instructions to avoid taking pexidartinib with a high-fat meal (approximately 55 to 65 grams of total fat)[2]

References

1. Daiichi Sankyo, Inc. Data on File.
2. Turalio. Prescribing Information. Daiichi Sankyo, Inc.; 2022.

A Better Understanding of the Effects of Meal Components and Intake Timing Will Help Inform Meal Recommendations to Patients

- What aspects of a meal have the greatest impact on pexidartinib exposure?



- When can a patient safely consume a high-fat meal in relation to pexidartinib dosing?

- A better understanding of the effects of meal components and intake timing will help inform meal recommendations to patients
  - What aspects of a meal (eg, caloric content, percent fat content, absolute fat content, or a combination of factors) have the greatest impact on pexidartinib exposure?
  - When can a patient safely consume a high-fat meal before or after pexidartinib dosing?

Development of a Physiologically Based Pharmacokinetic (PBPK) Model for Pexidartinib to Evaluate the Impact of Meal Contents and Intake Timing on Drug Exposure

American Conference on Pharmacometrics Meeting 2022

Shintaro Nakayama,[1]* Viera Lukacova,[2] Shuichi Tanabe,[3] Akiko Watanabe,[1] Jim Mullin,[2] Sandra Suarez-Sharp,[2] Takako Shimizu[1]

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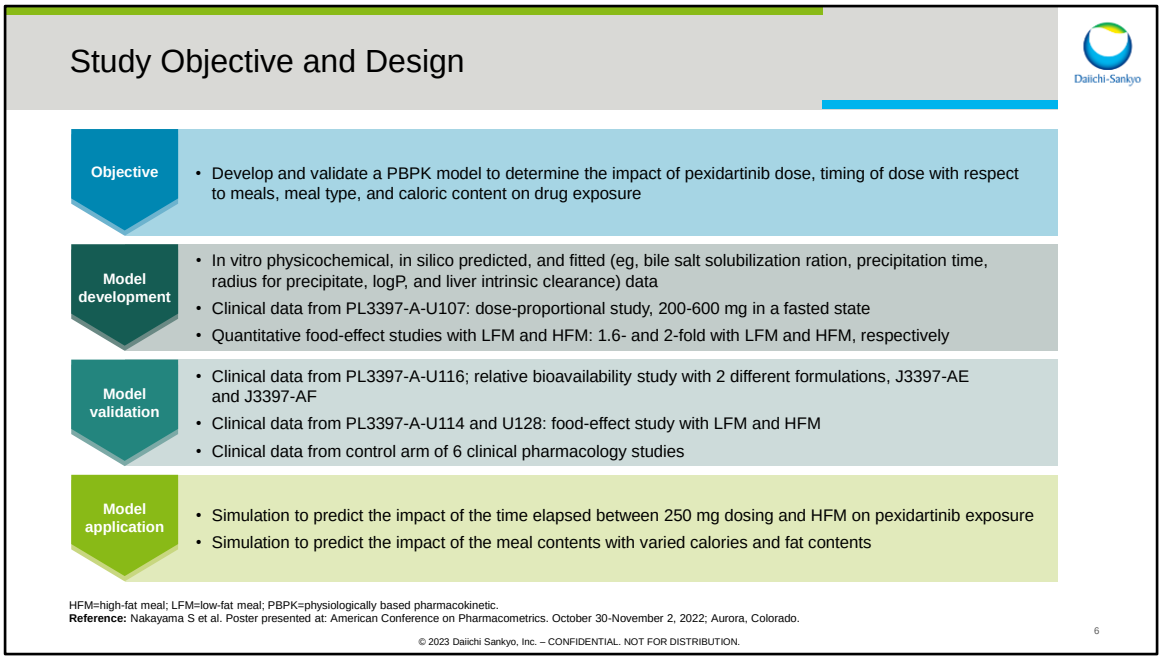
*Presenting author.



- The objective of this study was to develop and validate a physiologically based pharmacokinetic (PBPK) model to determine the impact of pexidartinib dose, timing of dose with respect to meals, meal type, and caloric content on drug exposure

Review figure on the slide.

Additional information:

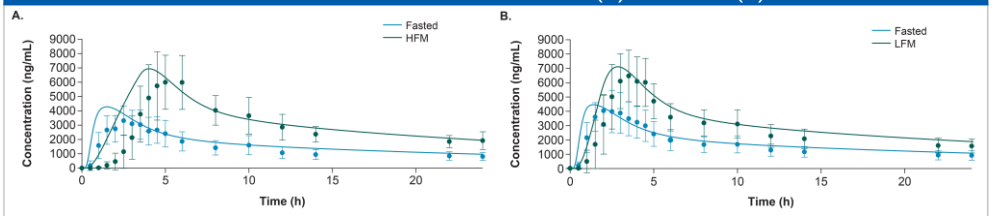
- The model was constructed in GastroPlus® (version 9.8.1, Simulations Plus, Inc.; Lancaster, CA, USA) using in vitro physicochemical properties, in silico predictions from ADMET Predictor® (version 10.0, Simulations Plus, Inc.; Lancaster, CA, USA), and in vivo parameters from pexidartinib clinical studies
- The Advanced Compartmental Absorption and Transit (ACAT™) model was used to mechanistically describe the intestinal absorption and first-pass extraction of pexidartinib after oral administration, and the PBPKPlus™ module in GastroPlus® was used to simulate the systemic distribution and clearance of pexidartinib

Reference

Nakayama S, Lukacova V, Tanabe S, et al. Development of a physiologically based pharmacokinetic (PBPK) model for pexidartinib to evaluate the impact of meal contents and intake timing on drug exposure. Poster presented at: American Conference on Pharmacometrics. October 30-November 2, 2022; Aurora, Colorado.

Model Validation[1]

Observed and Simulated PK Profiles for Pexidartinib After Administration in the Fasted State and With a HFM* (A) or a LFM† (B)



Observed points and error bars represent mean and 1 standard deviation. Circles represent observed values, and the line is simulated.

Predicted vs Observed Food Effect on the PK of Pexidartinib

Study	Dose (mg)	Meal type	Observed food effect‡		Predicted food effect		Predicted/ observed	
			C_{max} ratio	AUC_{inf}	C_{max} ratio	AUC_{inf}	C_{max} ratio	AUC_{inf}
PL3397-A-U114	400	HFM	1.99	2.11	1.62	1.90	0.82	0.90
PL3397-A-U128	400	LFM	1.56	1.59	1.59	1.69	1.02	1.07

Comparison of the observed and predicted values showed that the model correctly captured the effect of a low- and high-fat meal on pexidartinib exposure

AUC_{inf}=area under the plasma concentration-time curve from the time of dosing extrapolated to infinity; C_{max}=maximum observed plasma drug concentration; HFM=high-fat meal; LFM=low-fat meal; PK=pharmacokinetics.
*A HFM consisted of 2 slices of toast with 2 pats of butter, 2 fried eggs, 2 strips of pork bacon, 4 oz of hash brown potatoes, and 240 mL of whole milk. [2]
†A LFM consisted of 8 ounces of 1% milk, 1 boiled egg, and 1 packet of instant flavored oatmeal with water.[3]
‡"Food effect" is described as the ratio of exposure parameter (C_{max} or AUC_{inf}) after administration with a meal versus administration in fasted subjects. Observed food effect was calculated as a ratio of geometric means of individual values with the 2 different treatments.
References: 1. Nakayama S et al. Poster presented at: American Conference on Pharmacometrics. October 30-November 2, 2022; Aurora, Colorado. **2.** Daiichi Sankyo, Inc. Data on File. PL3397-A-U128 Clinical Study Report. **3.** Daiichi Sankyo, Inc. Data on File. PL3397-A-U114 Clinical Study Report.

- The model was validated by predicting pexidartinib exposure from 9 clinical studies. Some of the prediction errors for model validation were >25%, which is a consequence of high-observed intersubject and interstudy variability in pexidartinib PK
- Observed and simulated plasma concentration-time profiles for pexidartinib from clinical studies PL3397-A-U114 (with a high-fat meal) and PL3397-A-U128 (with a low-fat meal) are shown on the slide
- The model correctly captured the food effect with low-fat meals and high-fat meals, making it suitable to evaluate the bioequivalence between the dosing of 250 mg pexidartinib (2 x 125 mg capsules) administered with a low-fat meal and 400 mg pexidartinib (2 x 200 mg capsules) administered in a fasted state
- The predicted effect of a meal on C_{max} and AUC_{inf} captured the observed food effect with a low-fat meal and a high-fat meal in clinical studies

Reference

Nakayama S, Lukacova V, Tanabe S, et al. Development of a physiologically based pharmacokinetic (PBPK) model for pexidartinib to evaluate the impact of meal contents and intake timing on drug exposure. Poster presented at: American Conference on Pharmacometrics. October 30-November 2, 2022; Aurora, Colorado.

Model Application: Timing of High-fat Meal Consumption on Pexidartinib Exposure

Consuming a HFM ≥3 Hours Before Dosing Had a Negligible Effect on Pexidartinib PK

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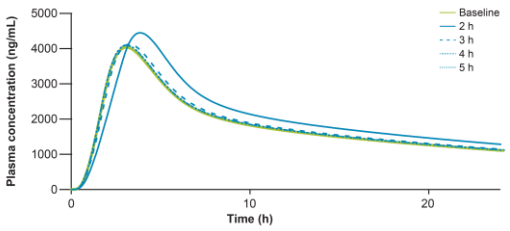
Impact on Pexidartinib Exposure When a HFM Was Consumed 2 to 5 Hours Before Administration of Pexidartinib + LFM



Green line (baseline) represents pexidartinib dosing with a LFM without earlier consumption of a HFM; blue lines show pexidartinib PK when a HFM is consumed 2 to 5 hours before dosing.

HFM before dosing	C_{max}		AUC_{inf}	
	(ng/mL)	Test/base*	(ng·h/mL)	Test/base*
Baseline	4039.0	–	78,346.4	–
2 h	4450.6	1.10	89,110.3	1.14
3 h	4121.6	1.02	80,580.0	1.03
4 h	4099.8	1.02	79,373.5	1.01
5 h	4097.9	1.01	79,322.0	1.01

Consumption of a high-fat meal

≥3 Hours Before — Negligible effect on exposure

2 Hours Before — Increases exposure by 10%-20%

AUC_{inf}=area under the plasma concentration-time curve up to time infinity; C_{max}=maximum plasma concentration; HFM=high-fat meal; h=hour; LFM=low-fat meal; PK=pharmacokinetics.
*Ratio of the PK parameter value between specific HFM timing and baseline (no HFM).
Reference: Nakayama S et al. Poster presented at: American Conference on Pharmacometrics. October 30-November 2, 2022; Aurora, Colorado.

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- When a high-fat meal was consumed 2 hours before dosing, pexidartinib exposure increased by 10%-20%, whereas there was a negligible impact when a high-fat meal was consumed ≥3 hours before pexidartinib and a low-fat meal

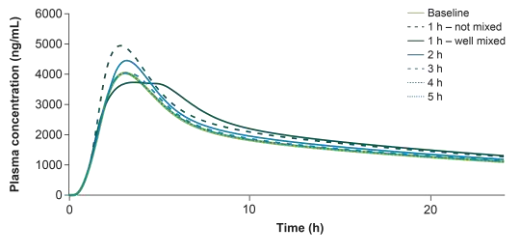
Reference

Nakayama S, Lukacova V, Tanabe S, et al. Development of a physiologically based pharmacokinetic (PBPK) model for pexidartinib to evaluate the impact of meal contents and intake timing on drug exposure. Poster presented at: American Conference on Pharmacometrics. October 30-November 2, 2022; Aurora, Colorado.

Consuming a HFM ≥2 Hours After Dosing Had a <10% Effect on Pexidartinib PK

Daiichi-Sankyo

Impact on Pexidartinib Exposure When a HFM Was Consumed 1 to 5 Hours After Administration of Pexidartinib + LFM



Green line (baseline) represents pexidartinib dosing with a LFM without subsequent consumption of a HFM; blue lines show pexidartinib PK when a HFM is consumed 2 to 5 hours after dosing.

HFM after dosing	C_{max}		AUC_{inf}	
	(ng/mL)	Test/base‡	(ng·h/mL)	Test/base‡
Baseline	4039.0	–	78,346.4	–
1 h – not mixed*	4942.2	1.22	90,352.3	1.15
1 h – well mixed†	3730.3	0.92	90,855.9	1.16
2 h	4451.9	1.10	83,819.4	1.07
3 h	4042.6	1.00	80,216.5	1.02
4 h	4039.0	1.00	78,745.1	1.01
5 h	4039.0	1.00	78,436.8	1.00

Consumption of a high-fat meal

≥2 Hours After — Increases exposure by <10%

1 Hour After — Increases exposure by 15%-16%

AUC_{inf}=area under the plasma concentration-time curve up to time infinity; C_{max}=maximum plasma concentration; h=hour; HFM=high-fat meal; LFM=low-fat meal; PK=pharmacokinetics.
*Result based on the assumption that HFM does not mix with the remaining stomach contents, and the remaining drug continues emptying from the stomach at the same rate as before the HFM consumption.
†Result based on the assumption that HFM is well mixed with the remaining stomach contents, resulting in a slower rate of the remaining drug emptying from the stomach.
‡Ratio of PK parameter value between specific HFM timing and baseline (no HFM).
Reference: Nakayama S et al. Poster presented at: American Conference on Pharmacometrics. October 30-November 2, 2022; Aurora, Colorado.

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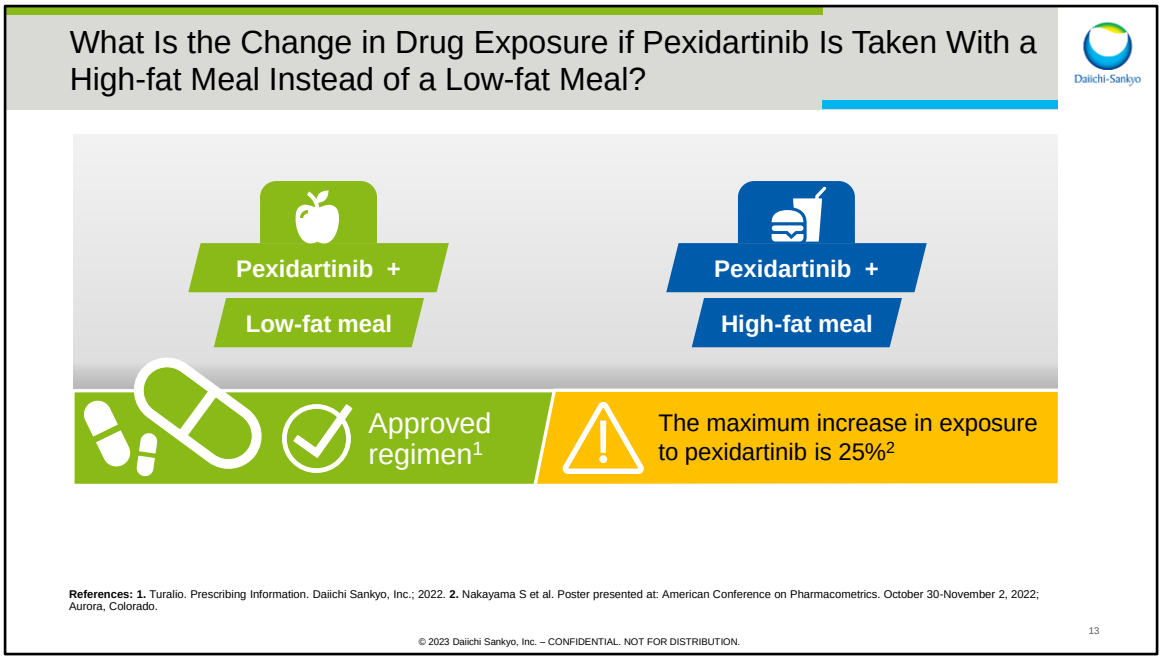
- A 15%-16% increase in percent absorbed, bioavailability, and AUC_{inf} was predicted when consuming a high-fat meal 1 hour after pexidartinib and a low-fat meal, but a <10% effect on PK was predicted when a high-fat meal was consumed ≥2 hours after pexidartinib and a low-fat meal

Reference

Nakayama S, Lukacova V, Tanabe S, et al. Development of a physiologically based pharmacokinetic (PBPK) model for pexidartinib to evaluate the impact of meal contents and intake timing on drug exposure. Poster presented at: American Conference on Pharmacometrics. October 30-November 2, 2022; Aurora, Colorado.



- Dosing pexidartinib with a high-fat meal is expected to show the maximum difference in exposure
- The model-predicted increase in drug exposure when dosing pexidartinib with a high-fat meal was only approximately 25% compared to dosing pexidartinib with a low-fat meal, which is consistent with a low impact of high-fat meals on pexidartinib exposure with the currently approved regimen

Reference

Nakayama S, Lukacova V, Tanabe S, et al. Development of a physiologically based pharmacokinetic (PBPK) model for pexidartinib to evaluate the impact of meal contents and intake timing on drug exposure. Poster presented at: American Conference on Pharmacometrics. October 30-November 2, 2022; Aurora, Colorado.

Model Application: Effect of Meal Components on Pexidartinib Exposure

Altering the Caloric Content of Food Does Not Significantly Affect Pexidartinib Exposure

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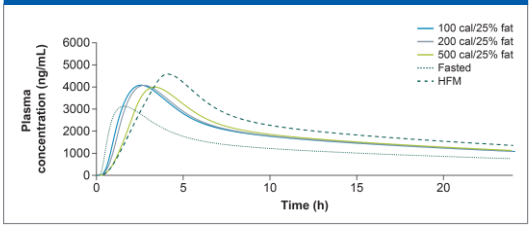
The Effect of Varying Calories on Pexidartinib Exposure



	C_{max}		AUC_{inf}	
	(ng/mL)	Test/base	(ng·h/mL)	Test/base
100 cal/25% fat	4083.0	1.02	77,505.0	0.98
200 cal/25% fat	4074.5	1.02	77,806.6	0.99
500 cal/25% fat	3994.7	–	78,708.6	–

- Altering the caloric content from 100 to 500 calories did not significantly alter AUC_{inf} and C_{max}
  - T_{max} changed by approximately 25%
- Meal recommendations focused on % fat content alone may be sufficient to ensure that the target level of pexidartinib exposure is achieved

AUC_{inf}=area under the plasma concentration-time curve from the time of dosing extrapolated to infinity; C_{max}=maximum observed plasma drug concentration; HFM=high-fat meal; T_{max}=time of maximum observed plasma drug concentration.
Reference: Nakayama S et al. Poster presented at: American Conference on Pharmacometrics. October 30-November 2, 2022; Aurora, Colorado.

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- Altering the caloric content from 100 to 500 calories did not significantly alter AUC_{inf} and C_{max}
  - T_{max} changed by approximately 25%
- Therefore, meal recommendations focused on percent fat content alone may be sufficient to ensure that the target level of pexidartinib exposure is achieved

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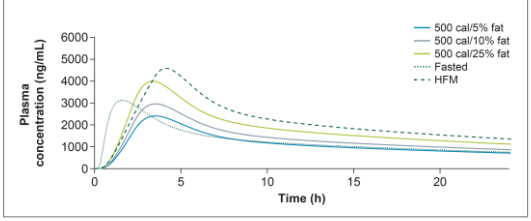
Nakayama S, Lukacova V, Tanabe S, et al. Development of a physiologically based pharmacokinetic (PBPK) model for pexidartinib to evaluate the impact of meal contents and intake timing on drug exposure. Poster presented at: American Conference on Pharmacometrics. October 30-November 2, 2022; Aurora, Colorado.

The Fat Content in a Meal Influences Pexidartinib Exposure

The Effect of Varying Fat Content on Pexidartinib Exposure



	C_{max}		AUC_{inf}	
	(ng/mL)	Test/base	(ng·h/mL)	Test/base
500 cal/5% fat	2409.0	0.60	49,377.6	0.63
500 cal/10% fat	2960.4	0.74	60,285.3	0.77
500 cal/25% fat	3994.7	–	78,708.6	–

- Changing the fat content between 5% and 25% resulted in an approximately 40% change in AUC_{inf} and C_{max}
- Meal recommendations based on calories alone would likely not be sufficient to ensure that the target pexidartinib exposure level is achieved

AUC_{inf}=area under the plasma concentration-time curve from the time of dosing extrapolated to infinity; C_{max}=maximum observed plasma drug concentration; HFM=high-fat meal.
Reference: Nakayama S et al. Poster presented at: American Conference on Pharmacometrics. October 30-November 2, 2022; Aurora, Colorado.

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The Absolute Fat Content in a Meal Influences Pexidartinib Exposure

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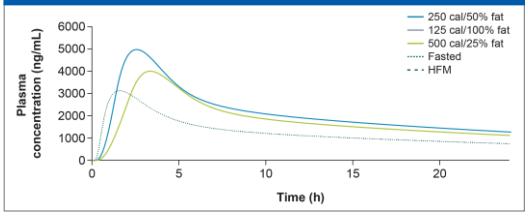
The Effect of Varying Calories and Absolute Fat Content on Pexidartinib Exposure



	C_{max}		AUC_{inf}	
	(ng/mL)	Test/base	(ng·h/mL)	Test/base
125 cal/100% fat	5649.1	1.41	96,964.4	1.23
250 cal/50% fat	4961.9	1.24	91,254.0	1.16
500 cal/25% fat	3994.7	–	78,708.6	–

- Changing the number of calories (125 cal-500 cal) and percent fat (25%-100%) changed AUC_{inf} by approximately 25% and C_{max} by approximately 40%
  - T_{max} was approximately 40% lower in the low-calorie/high-fat meal compared to the high-calorie/low-fat meal condition
- Meal recommendations based on absolute fat content alone would likely not be sufficient to ensure that the target pexidartinib exposure level is achieved

AUC_{inf}=area under the plasma concentration-time curve from the time of dosing extrapolated to infinity; C_{max}=maximum observed plasma drug concentration; HFM=high-fat meal.
Reference: Nakayama S et al. Poster presented at: American Conference on Pharmacometrics. October 30-November 2, 2022; Aurora, Colorado.

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  - T_{max} was approximately 40% lower in the low-calorie/high-fat meal compared to the high-calorie/low-fat meal condition
- Therefore, meal recommendations based on absolute fat content alone would likely not be sufficient to ensure that the target pexidartinib exposure level is achieved

Reference

Nakayama S, Lukacova V, Tanabe S, et al. Development of a physiologically based pharmacokinetic (PBPK) model for pexidartinib to evaluate the impact of meal contents and intake timing on drug exposure. Poster presented at: American Conference on Pharmacometrics. October 30-November 2, 2022; Aurora, Colorado.

Conclusions

The fat percentage of a meal qualitatively increased the exposure of pexidartinib, suggesting the importance of controlling food components, especially fat contents, and meal timing before/after pexidartinib administration

The predicted low impact of consuming a high-fat meal before or after pexidartinib dosing with a low-fat meal is consistent with only a 25% observed difference in pexidartinib exposure when administered with a low-fat meal or high-fat meal

These results can be used to derive recommendations on the timing of pexidartinib dose administration with respect to meals

Reference: Nakayama S et al. Poster presented at: American Conference on Pharmacometrics. October 30-November 2, 2022; Aurora, Colorado.

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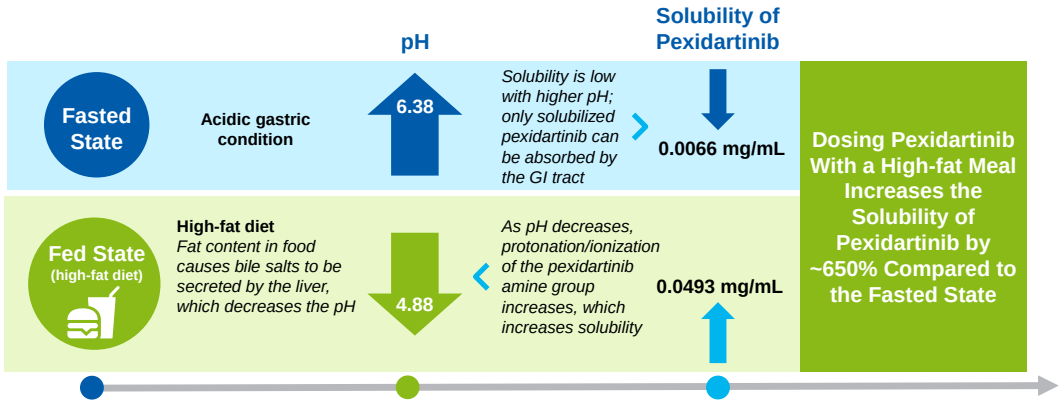
Backup Slides

Implications of Dosing With a High-fat Meal vs Fasted State on the Relative Oral Bioavailability of Pexidartinib

- **The solubility of pexidartinib is pH-dependent**
- **A high-fat diet lowers the pH, which makes pexidartinib more soluble, and more of the dose can be absorbed**



GI=gastrointestinal.
Reference: Daiichi Sankyo, Inc. Data on File.

Effects of Different Meal Types on Pexidartinib Pharmacokinetics in Healthy Patients: Study Design

Eligible patients were 18 to 45 years of age (high-fat meal study) or 18 to 60 years of age (low-fat meal study) and in good health

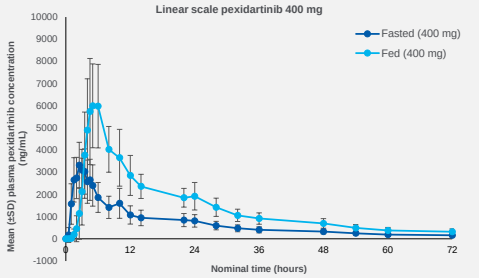
	High-fat meal 800-1000 kcal with ~50% of calories from fat	Low-fat meal 400-500 kcal with ~25% of calories from fat
Treatment	**Pexidartinib phase 3 formulation:** 400 mg administered orally on Day 1 within 30 minutes of a high-fat, high-calorie meal	**Pexidartinib phase 3 formulation:** 400 mg administered orally on Day 1 within 30 minutes of low-fat, low-calorie meal
Outcomes	AUC, C_{max}, and mean (SD) plasma concentration of pexidartinib	AUC, C_{max}, mean (SD) plasma concentration of pexidartinib

AUC=area under curve; C_{max}=peak pexidartinib concentration; SD=standard deviation.
Zahir et al. Poster presented at: American College of Clinical Pharmacology® (ACCP) Annual Meeting; September 21-23, 2020; Virtual.

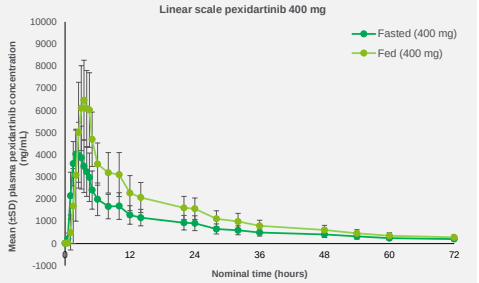
Effects of Different Meal Types on Pexidartinib Pharmacokinetics in Healthy Patients: High-fat Versus Low-fat Meal

- Pexidartinib administered after a **high-fat meal** resulted in an approximate **doubling of C_{max} and AUC** compared with the fasted state for doses ranging from 400 mg to 1800 mg
- Pexidartinib administered (200 mg and 400 mg) with **a low-fat meal increased exposure by ~60%**

High-fat Meal Study Mean (±SD) Plasma Pexidartinib Concentration-Time Profiles by treatment



Low-fat Meal Study Mean (±SD) Plasma Pexidartinib Concentration-Time Profiles by treatment



AUC=area under curve; C_{max}=peak pexidartinib concentration; SD=standard deviation.
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