Clinical Study Protocol Addendum Version (1) I8F-JE-GPGO

A Phase 3 Study of Tirzepatide Monotherapy Compared to Dulaglutide 0.75 mg in Patients with Type 2 Diabetes Mellitus (SURPASS J-mono)

NCT03861052

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1. Protocol Addendum I8F-JE-GPGO(1) A Phase 3 Study of Tirzepatide Monotherapy Compared to Dulaglutide 0.75 mg in Patients with Type 2 Diabetes Mellitus (SURPASS J-mono)

Tirzepatide (LY3298176)

This addendum is to be performed in addition to all procedures required by protocol I8F-JE-GPGO or any subsequent amendments to that protocol.

Eli Lilly Japan K.K
Kobe, Hyogo, Japan

Protocol Addendum (1) Electronically Signed and Approved by Lilly on date provided below.

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3. Rationale for Addendum

The Japan guidance for Clinical Pharmacokinetic Studies of Pharmaceutics (IYAKUSHIN HATSU No.796. 2001) states that pharmacokinetic (PK) studies using the final formulation need to be conducted prior to submission of the new drug application (NDA). To meet this regulatory requirement in Japan, the PK of tirzepatide after single and multiple subcutaneous doses of tirzepatide using the commercial formulation will be evaluated in Japanese patients with type 2 diabetes mellitus (T2DM).

The concentration-time profile and conventional PK parameters of tirzepatide have been characterized in a Phase 1 study in Japanese patients with T2DM (I8F-JE-GPGC) using an early phase lyophilized formulation. Currently, no PK data have been generated in Japanese patients using the commercial solution formulation supplied in a single use pen, which is the formulation to be evaluated in Phase 3 in Japanese patients with T2DM.

In the Phase 1 study of tirzepatide in Japanese patients with T2DM, a meal tolerance test (MTT) was not performed and postprandial glucose metabolic hormones were not assessed. These data are frequently requested by healthcare providers. In addition, continuous glucose monitoring (CGM) will be performed in order to show reducing daily variability of blood glucose level.

Body composition will be measured in order to confirm that majority of weight loss is due to fat mass reduction.

This addendum is to be performed in patients at certain participating sites for PK, glucodynamic, and pharmacodynamics (PD) evaluation in Protocol I8F-JE-GPGO (GPGO), which is a Phase 3 study in Japan. The objectives of this addendum are to evaluate:

1) the PK profile of tirzepatide in Japanese patients with T2DM at the dose level of 5 mg, 10 mg, and 15 mg of tirzepatide at the first dose (Week 0) and steady state (Week 32) using the commercial formulation
2) detailed 6-hour postprandial data, including serum glucose profiles, insulin, C-peptide, glucagon, triglycerides, and satiety at Week 32
3) continuous glycemic parameters immediately after the start of administration and at Week 32
4) body composition, including total body water, protein, minerals, body fat mass, and lean body mass at Weeks 12, 32, and 52

These outcomes will provide supportive data to understand the mechanism of action of tirzepatide, and to answer the frequently asked questions by healthcare providers.

4. Protocol Additions

4.1. Schedule of Activities

Table GPGO.1. Schedule of Activities, I8F-JE-GPGO

	Screening	Lead-in		Treatment																	Follow-up
Study Visit	**1**	**2**		**3**					**4 - 5**	**6**	**7-9**		**10**					**11-12**	**13**	**ET**	**801**
Week of Treatment	—	—	**-1**	**0**	—	—	—	**1**	—	**12**	—	**31**	**32**	—	—	—	**33**	—	**52**	—	—
Hour of Treatment			—	0	8	24	48	72	168		—		—	0	8	24	48	72	168		—		
Visit Window for PK (hour)			—	—	±1	±2	±4	±7	±16	-	—		—	—	±1	±2	±4	±7	±16		—		
Laboratory Tests																							
Tirzepatide PK sample for commercial formulation PK				X	X	X	X	X	X					X	X	X	X	X	X				

	Screening	Lead-in		Treatment																	Follow-up
Study Visit	**1**	**2**		**3**					**4 - 5**	**6**	**7-9**		**10**					**11-12**	**13**	**ET**	**801**
Week of Treatment	—	—	**-1**	**0**	—	—	—	**1**	—	**12**	—	**31**	**32**	—	—	—	**33**	—	**52**	—	—
Day of Treatment			-7[c]	0	—	—	—	7[c]		—		-7[d]	0	—	—	—	7[d]		—		
Visit Window for CGM and MTT (day)			—	—	—	—	—	0 to +1	-	—		0 to +3	—	—	—	—	0 to +1		—		
Clinical Assessments																					
Body Composition				X[e]						X			X						X		
Laboratory Tests																					
CGM insertion[a]			X									X									
CGM removal[a]								X									X				
Meal tolerance test[b]			X										X								

Abbreviations: CGM = continuous glucose monitoring; ET = early termination; MTT = meal tolerance test; PK = pharmacokinetics.

[a] CGM device to be applied on Day -7, and device removed on Day 7 at Week 0 and Week 32. Although the CGM device will be applied from Day -7 through Day 7 at Week 0 and Week 32, the data required to be analyzed is from Day -6 through Day 6.

[b] MTT samples to be collected at 0 (pre-meal), 30, 60, 90, 120, 180, 240, 300, and 360 minutes after the start of standardized test meal at Week -1 (Day-7 of Week 0) and Week 32. The laboratory tests for MTT include serum glucose, insulin, c-peptide, glucagon, and triglyceride. A perception of satiety (full and hungry) visual analog scale (VAS) should be completed by patients at 0 (pre-meal), 60, 120, 180, 240, 300, and 360 minutes following the standardized test meal on each MTT day.

[c] Relative to Week 0.

[d] Relative to Week 32.

[e] The body composition should be measured prior to administration of investigational product.

4.2. Objectives and Endpoints

Table GPGO.2 shows the objectives and endpoints of this addendum, which are in addition to the Study GPGO protocol body.

Table GPGO.2. Objectives and Endpoints

Objectives	Endpoints
Pharmacokinetics	
• To evaluate the pharmacokinetic profile of once-weekly tirzepatide in Japanese patients with T2DM using the commercial formulation	• AUC and C_{max} of tirzepatide
Exploratory	
• To compare the effect of once-weekly tirzepatide versus dulaglutide 0.75 mg on the pharmacodynamic profile and satiety after a standardized test meal at Week 32	• The change from baseline in serum glucose $AUC_{(0-6h)}$ • The change from baseline in insulin $AUC_{(0-6h)}$ • The change from baseline in C-peptide $AUC_{(0-6h)}$ • The change from baseline in glucagon $AUC_{(0-6h)}$ • The change from baseline in triglyceride $AUC_{(0-6h)}$ • The change from baseline in satiety (full and hungry) in VAS
• To compare the effect of once-weekly tirzepatide versus dulaglutide 0.75 mg on daily glucose variability measured by CGM at Week 32	• Daily average glucose (mg/dL) • Time in range ≤70 mg/dL (minutes) • Time in range >180 mg/dL (minutes) • Daily within-day SD (mg/dL) • Daily MAGE (mg/dL)
• To compare the effect of once-weekly tirzepatide versus dulaglutide 0.75 mg on body composition at Week 12, 32, and 52	• The change from baseline in total body water (L) • The change from baseline in protein (kg) • The change from baseline in minerals (kg) • The change from baseline in body fat mass (kg) • The change from baseline in lean body mass (kg)

Abbreviations: AUC = area under the concentration versus time curve; $AUC_{(0-6h)}$ = area under the concentration versus time curve from time zero to 6 hours after dose; C_{max} = maximum concentration; CGM = continuous glucose monitoring; MAGE = mean amplitude of glycemic excursion; T2DM = type 2 diabetes mellitus; VAS = visual analog scale.

4.3. Study Design

4.3.1. *Overall Design*

Study GPGO is a multicenter, randomized, double-blind, parallel, active-controlled, 52-week Phase 3 study which will assess the safety and efficacy of tirzepatide (5, 10, and 15 mg), compared to dulaglutide 0.75 mg in approximately 636 randomized patients with T2DM who have discontinued oral antihyperglycemic medication (OAM) monotherapy or are OAM-naïve.

Study GPGO will consist of 3 periods: a 4-week (OAM-naïve) or 10-week (at least 8-week OAM washout) screening/lead-in period, followed by a 52-week treatment period, and a 4-week safety follow-up period. Patients will be randomized in a 1:1:1:1 ratio (tirzepatide 5 mg, 10 mg, 15 mg, and dulaglutide 0.75 mg).

Patients will be stratified based on baseline glycated hemoglobin (HbA1c) (≤8.5% and >8.5%), baseline body mass index (BMI) (<25 or ≥25 kg/m^2), and washout of antidiabetic medication (yes or no).

For the PK profile, PK samples will be collected at pre-dose, 8, 24, 48, 72, and 168 hours at Week 0 and Week 32.

For the glucodynamic and PD evaluation, MTT will be performed at Week -1 (Day-7 of Week 0) and Week 32. Time points for blood sampling will be 0 (pre-meal), 30, 60, 90, 120, 180, 240, 300, and 360 minutes after the start of standardized test meal. Satiety will be also assessed at 0 (pre-meal), 60, 120, 180, 240, 300, and 360 minutes after the start of standardized test meal. Investigational product material will be administered before starting standardized test meal at Week 32. Continuous glucose monitoring will be initiated on Day -7, and will end on Day 7 at Week 0 and Week 32.

Body composition will be assessed at Weeks 0, 12, 32, and 52. Every effort should be made to measure body composition in the same condition at each time point to minimize intra-individual variability.

4.3.2. *Number of Participants*

The total number of participants for this addendum is approximately 48 patients, which is based on the objectives of PK and glucodynamic effect.

To evaluate the glucodynamic effect, a total of 48 participants (12 participants per treatment) will be needed. The assumptions for this sample size are described in Section 4.5.1. To provide the PK and pharmacodynamic (PD) evaluation similar to the historical conventional Phase 1 studies, samples from approximately 10 patients in the treatment arms of tirzepatide 5 mg, 10 mg, 15 mg, and/or dulaglutide 0.75 mg will be needed.

4.3.3. *Scientific Rationale for Study Design*

This addendum is designed to evaluate PK, glucodynamic, and PD effects after a standardized test meal. Patients with T2DM who have diet and exercise therapy only will be enrolled to exclude the background effect of other antidiabetic agents. A Japanese standardized test meal (480 kcal, carbohydrate: protein: fat = 2.8:1:1) was selected because it was used in the previous MTTs conducted in Japan (Lee et al. 2010; Yabe et al. 2010; Yabe et al. 2015).

Pharmacokinetic samples will be collected at Week 0 and Week 32 to enable the evaluation of the PK of tirzepatide after a single dose and at steady state for all treatment arms.

Continuous glucose monitoring will be performed on Day -7 through Day 7 at Week 0 and Week 32, and MTT will be performed at Week -1 (Day-7 of Week 0) and Week 32, which are to enable the evaluation of tirzepatide at steady state for all treatment arms.

Body composition will be measured at Weeks 0, 12, 32, and 52 to enable evaluating time course of change of body composition during the study period. The time point was determined based on the reference data in combination of luseogliflozin and liraglutide (Seino et al. 2018). In the study described in the reference, time points were 0, 4, 12, 24, and 52 weeks.

4.3.4. *Lifestyle and/or Dietary Requirements*

4.3.4.1. Meals and Dietary Restrictions

Study participants should be instructed to continue diet therapy during the study period. Study participants must be fasting at least 10 hours before intake of a test meal for the MTT.

4.4. Study Assessments and Procedures

Section 4.1 lists the Schedule of Activities, detailing the study procedures and their timing.

Attachment 1 lists the laboratory tests that will be performed for the MTT.

Attachment 2 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

Attachment 3 provides a summary of MTT procedures.

4.4.1. *Pharmacokinetics*

In the historical conventional Phase 1 study, the PK of tirzepatide was evaluated in approximately 12 Japanese subjects per treatment arm with a different titration regimen from Phase 3 studies. This study intends to obtain PK data from approximately 10 patients per treatment arm; PK samples will be collected from 12 patients in each of the treatment arms of tirzepatide (5-mg, 10-mg, and 15-mg arms) and the dulaglutide 0.75-mg arm.

The samples for drug concentration measurements will be handled in accordance with the sponsor-specified procedures.

Blood samples for PK evaluation will be collected from certain patients at participating site(s) during the study at Week 0 and Week 32. Blood sampling will be performed at the times specified in the Study Schedule of Activities (Section 4.1).

Plasma samples for drug concentration measurements will be analyzed at a laboratory approved by the Sponsor. Pharmacokinetic samples will be collected from patients allocated to the dulaglutide arm but the samples will not be assayed for dulaglutide concentration.

Drug concentration information will not be reported to investigative sites or to other blinded personnel until study completion. To preserve the blinding of the study, a minimum number of Lilly personnel will see these results before study completion.

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following the last patient visit for the study, because re-assay may be required, based on the results of the PK analysis.

4.4.2. *Meal Tolerance Test*

4.4.2.1. Pharmacodynamics

At times specified in the Schedule of Activities (Section 4.1) and Attachment 3, venous blood samples will be collected and used to determine the PD effects of tirzepatide. Blood will be collected by venipuncture in order to evaluate fasting serum glucose, postprandial serum glucose, insulin, C-peptide, glucagon, and triglyceride and will be analyzed in the central laboratory.

The following measures of PD will be evaluated:

- The change from baseline in serum glucose area under the concentration versus time curve from time zero to 6 hours ($AUC_{[0\text{-}6h]}$) at Week 32
- The change from baseline in insulin (30, 60, 90, 120, 180, 240, 300, and 360 minutes) at Week 32
- The change from baseline in insulin $AUC_{(0\text{-}6h)}$ at Week 32
- The change from baseline in C-peptide (30, 60, 90, 120, 180, 240, 300, and 360 minutes) at Week 32
- The change from baseline in C-peptide $AUC_{(0\text{-}6h)}$ at Week 32
- The change from baseline in glucagon (30, 60, 90, 120, 180, 240, 300, and 360 minutes) at Week 32
- The change from baseline in glucagon $AUC_{(0\text{-}6h)}$ at Week 32
- The change from baseline in triglyceride (30, 60, 90, 120, 180, 240, 300, and 360 minutes) at Week 32
- The change from baseline in triglyceride $AUC_{(0\text{-}6h)}$ at Week 32

4.4.2.2. Satiety after Standardized Test Meal

A perception of satiety (full and hungry) visual analog scale (VAS) should be completed by patients at 0 (pre-meal), 60, 120, 180, 240, 300, and 360 minutes following the standardized test meal on each MTT day.

4.4.3. *Continuous Glucose Monitoring*

The CGM data will complement the evaluation of the glucodynamic effects of tirzepatide (5 mg, 10 mg, and 15 mg) at Week 0 and Week 32.

The FreeStyle Libre Pro system (Abbott) will be used for CGM in this study. The CGM sensor will be applied to the patients at the clinic on Day -7, and will be removed on Day 7 at Week 0 and Week 32.

The CGM sensors will be scanned during clinic visits, and data from the CGM device will be uploaded to a central vendor's secure location. Mechanisms to blind the CGM data during the sensor scanning and data upload process are not deemed to be necessary, because this study

compares the study drug to an active comparator (dulaglutide). Data will be transmitted from the central vendor to Lilly at determined intervals.

4.4.4. *Body Composition*

Total body water (L), protein (kg), minerals (kg), and body fat mass (kg) will be measured by InBody 770 (Inbody Japan) at Weeks 0, 12, 32, and 52. The lean body mass (kg) will be calculated based on total body water, protein, and minerals (Section 4.5.2.4).

4.5. Statistical Considerations and Data Analysis

4.5.1. *Sample Size Determination*

A total of 48 patients will be randomized in a 1:1:1:1 ratio to 1 of 4 treatments. Assuming 1 dropout, the sample size of 11 patients for each treatment group would provide 79% power to demonstrate a statistically significant difference between the tirzepatide dose levels and dulaglutide 0.75 mg. This computation assumes the true treatment difference in glucose $AUC_{(0\text{-}6h)}$ is 330 mg*hr/dL, a common standard deviation of 250 mg*hr/dL.

4.5.2. *Statistical Analyses*

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designee. Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) or the clinical study report (CSR). Additional exploratory data analyses may be conducted, as deemed appropriate.

4.5.2.1. Pharmacokinetic Analyses

All tirzepatide concentration data will be analyzed using noncompartmental methods implemented with the program WinNonlin on a computer that meets or exceeds the minimum system requirements. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation. It is possible that other validated software programs may be utilized, if appropriate, warranted, and approved by Global PK/PD/TS management.

The primary parameters to be estimated will be maximum concentration (C_{max}), time of maximum observed concentration (t_{max}) and area under the concentration-time curve (AUC) of tirzepatide at Week 0 and Week 32. Other noncompartmental PK parameters, such as half-life ($t_{1/2}$) apparent clearance (CL/F) and apparent volume of distribution (V/F) may be estimated, if deemed appropriate.

4.5.2.2. Pharmacodynamic Analyses

4.5.2.2.1. Pharmacodynamic Parameter Estimation

Pharmacodynamic parameters will be calculated for glucose, insulin, glucagon, C-peptide, and triglyceride data following the standardized test meal at Week -1 (Day-7 of Week 0) and Week 32. The $AUC_{(0\text{-}6h)}$ will be calculated using the linear-trapezoidal method. The

parameters area under the concentration versus time curve from time zero to 1 hour ($AUC_{[0-1h]}$), area under the concentration versus time curve from time zero to 2 hours ($AUC_{[0-2h]}$), area under the concentration versus time curve from time zero to 3 hours ($AUC_{[0-3h]}$), area under the concentration versus time curve from time zero to 4 hours ($AUC_{[0-4h]}$), and area under the concentration versus time curve from time zero to 5 hours ($AUC_{[0-5h]}$) may also be calculated.

All PD parameters will be summarized by treatment group and listed.

4.5.2.2.2. Pharmacodynamic Statistical Inference

Pharmacodynamic analyses will be conducted using data from all patients who receive at least 1 dose of the investigational product and have evaluable PD.

The change in PD parameters from baseline to Week 32 will be analyzed by an analysis of covariance (ANCOVA) model with treatment, baseline BMI group (<25 or ≥25 kg/m^2) and washout of antidiabetic medication (yes or no) and baseline value (Week -1 [Day-7 of Week 0]) of the dependent variable as a covariate. The least-squares mean (LS Mean), standard error (SE) and the 95% confidence interval (CI) derived from the model will be displayed for change from baseline by treatment group. Treatment comparisons will be displayed showing the treatment difference LS Mean and the 95% CI of treatment differences along with the p-values for the treatment comparison. Statistical tests will be conducted using 2-sided tests and a significance level of 0.05. No multiplicity adjustment will be applied.

4.5.2.3. Continuous Glucose Monitoring Analyses

The CGM data from Day -6 to Day 6 at 2 occasions (Week 0 and Week 32) will be summarized and analyzed. The CGM parameters (daily average, daily standard deviation, daily mean amplitude of glycemic excursion [MAGE], daily time in range [≤70 mg/dL or ≥180 mg/dL]) will be derived from glucose data collected by a CGM device and will be summarized by treatment and day for each occasion. The baseline CGM parameters will be derived from the data measured prior to administration of investigational product. A comparison between tirzepatide doses and dulaglutide 0.75 mg will be conducted. Individual (by patient) or mean by treatment, glucose data will be plotted, if deemed appropriate.

4.5.2.4. Body Composition Analyses

The data of total body water, protein, minerals, and body fat mass will be collected. Lean body mass will be derived as the sum of 3 components (total body water, protein, and minerals). Change in body composition parameters (body weight, total body water, protein, minerals, body fat mass, and lean body mass) from baseline will be summarized. A comparison between tirzepatide doses and dulaglutide 0.75 mg will be conducted.

4.5.2.5. Analyses for Satiety Evaluation

Satiety after a standardized test meal (Satiety, Hunger and Satiety/Hunger) in the VAS will be summarized by treatment and time after a standardized test meal (0 [pre-meal], 60, 120, 180, 240, 300, and 360 minutes). A comparison of tirzepatide doses and dulaglutide 0.75 mg will be conducted.

5. References

IYAKUSHIN HATSU No.796. Clinical Pharmacokinetic Studies of Pharmaceuticals. June 1, 2001

Lee S, Yabe D, Nohtomi K, Takada M, Morita R, Seino Y, Hirano T. Intact glucagon-like peptide-1 levels are not decreased in Japanese patients with type 2 diabetes. *Endocr J*. 2010;57(2):119-126.

Seino Y, Yabe D, Sasaki T, Fukatsu A, Imazeki H, Ochiai H, Sakai S. Sodium-glucose cotransporter-2 inhibitor luseogliflozin added to glucagon-like peptide 1 receptor agonist liraglutide improves glycemic control with bodyweight and fat mass reductions in Japanese patients with type 2 diabetes: a 52-week, open-label, single-arm study. *J Diabetes Investig*. 2018;9(2):332-340.

Yabe D, Kuroe A, Watanabe K, Iwasaki M, Hamasaki A, Hamamoto Y, Harada N, Yamane S, Lee S, Murotani K, Deacon CF, Holst JJ, Hirano T, Inagaki N, Kurose T, Seino Y. Early phase glucagon and insulin secretory abnormalities, but not incretin secretion, are similarly responsible for hyperglycemia after ingestion of nutrients. *J Diabetes Complications*. 2015;29(3):413-421.

Attachment 1. Protocol Addendum GPGO(1) Clinical Laboratory Tests

Safety Laboratory Tests, Protocol Addendum I8F-JE-GPGO(1)

Meal tolerance test (0, 30, 60, 90, 120, 180, 240, 300, and 360 minutes)
Serum Glucose
Insulin
C-peptide
Glucagon
Triglycerides

Note: The meal tolerance test includes the following tests: serum glucose, insulin, C-peptide, glucagon, and triglycerides.

Attachment 2. Protocol Addendum GPGO(1) Blood Sampling Summary

This table summarizes the approximate blood volumes for all blood sampling during the study.

Sampling Summary, Protocol Addendum I8F-JE-GPGO(1)

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Tirzepatide PK sample for commercial formulation PK	3	12	36
MTT (serum glucose, insulin, C-peptide, glucagon, and triglyceride)	8	18	144
Total	-	-	180

Abbreviations: MTT = meal tolerance test; PK = pharmacokinetics.

Attachment 3. Protocol Addendum GPGO(1) Meal Tolerance Test

Meal Tolerance Test, Protocol Addendum I8F-JE-GPGO(1)

Time	Procedure
Before MTT	All evaluations for a regular visit
	Blood sampling for serum glucose, insulin, C-peptide, glucagon, and triglyceride (for 0 min) Satiety evaluation (VAS) (for 0 min)
	Dose of investigational product at Week 32
0 min	Start standardized test meal[c]
30 min[a]	Blood sampling for serum glucose, insulin, C-peptide, glucagon, and triglyceride
60 min[a]	Blood sampling for serum glucose, insulin, C-peptide, glucagon, and triglyceride Satiety evaluation (VAS)
90 min[a]	Blood sampling for serum glucose, insulin, C-peptide, glucagon, and triglyceride
120 min[a]	Blood sampling for serum glucose, insulin, C-peptide, glucagon, and triglyceride Satiety evaluation (VAS)
180 min[b]	Blood sampling for serum glucose, insulin, C-peptide, glucagon, and triglyceride Satiety evaluation (VAS)
240 min[b]	Blood sampling for serum glucose, insulin, C-peptide, glucagon, and triglyceride Satiety evaluation (VAS)
300 min[b]	Blood sampling for serum glucose, insulin, C-peptide, glucagon, and triglyceride Satiety evaluation (VAS)
360 min[b]	Blood sampling for serum glucose, insulin, C-peptide, glucagon, and triglyceride Satiety evaluation (VAS)

Abbreviations: min = minutes; MTT = meal tolerance test; VAS = visual analog scale.

[a] For each time point, ±5 minutes for sampling window is allowed.

[b] For each time point, ±10 minutes for sampling window is allowed.

[c] A Japanese standard test meal (480 kcal, carbohydrate: protein: fat = 2.8:1:1) should be ingested within 15 minutes.

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