Clinical trial results:
Influence of a fatty beverage (Milk) on the absorption of erlotinib: a randomized, cross-over pharmacokinetic study (MERLOT-study)

Summary

EudraCT number	2016-001597-15
Trial protocol	NL
Global end of trial date	27 December 2019

Results information

Result version number	v1 (current)
This version publication date	24 November 2021
First version publication date	24 November 2021
Summary attachment (see zip file)	Published paper MERLOT study (2021 Clin Pharmacokinet Influence of Cow's Milk and Esomeprazole on the Absorption of Erlotinib.pdf)

Trial information

Trial identification

Sponsor protocol code	MERLOT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Erasmus MC cancer institute
Sponsor organisation address	Molewaterplein 40, Rotterdam, Netherlands, 3015 GD
Public contact	A.H.J. Mathijssen, Erasmus MC cancer institute, a.mathijssen@erasmusmc.nl
Scientific contact	A.H.J. Mathijssen, Erasmus MC cancer institute, a.mathijssen@erasmusmc.nl

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 December 2019
Global end of trial reached?	Yes
Global end of trial date	27 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective: To determine the influence of the fatty beverage Milk on the systemic exposure (AUC) to erlotinib in patients with or without concomitant use of a PPI.

Protection of trial subjects:

Study protocol was authorized by the local ethics committee

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 February 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	13
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients on active treatment with erlotinib

Pre-assignment

Screening details:

Checking for the in- and exclusion criteria (see protocol/paper/EudraCT form)

Period 1

Period 1 title	Overall trial
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

NA

Arms

Are arms mutually exclusive?	Yes
Arm title	arm 1

Arm description:

phase A: intake without water
phase B: intake with 250 ml milk

Arm type	cross-over arm
Investigational medicinal product name	Full milk
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Milk, 250ml every day taken concomitant with erlotinib

Arm title	arm 2

Arm description:

phase A: intake with water + PPI
phase B: intake with 250ml milk + PPI

Arm type	cross-over arm

No investigational medicinal product assigned in this arm

Number of subjects in period 1	arm 1	arm 2
Started	15	15
Completed	15	15

Period 2	
Period 2 title	baseline
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded
Blinding implementation details: NA	

Arms	
Are arms mutually exclusive?	Yes
Arm title	arm 1
Arm description: phase A: intake without water phase B: intake with 250 ml milk	
Arm type	cross-over arm
Investigational medicinal product name	Full milk
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use
Dosage and administration details: Milk, 250ml every day taken concomitant with erlotinib	
Arm title	arm 2
Arm description: phase A: intake with water + PPI phase B: intake with 250ml milk + PPI	
Arm type	cross-over arm
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	arm 1	arm 2
Started	15	15
Completed	15	15

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	30	30	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	67.5		
inter-quartile range (Q1-Q3)	55 to 73.5	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	20	20	

End points

End points reporting groups

Reporting group title	arm 1
Reporting group description:	
phase A: intake without water phase B: intake with 250 ml milk	
Reporting group title	arm 2
Reporting group description:	
phase A: intake with water + PPI phase B: intake with 250ml milk + PPI	
Reporting group title	arm 1
Reporting group description:	
phase A: intake without water phase B: intake with 250 ml milk	
Reporting group title	arm 2
Reporting group description:	
phase A: intake with water + PPI phase B: intake with 250ml milk + PPI	

Primary: Change in Area Under the erlotinib plasma concentration Curve (AUC)

End point title	Change in Area Under the erlotinib plasma concentration Curve (AUC)
End point description:	
End point type	Primary
End point timeframe:	
geomean AUC arm A vs geomean AUC arm B	

End point values	arm 1	arm 2	arm 1	arm 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	15	15	15
Units: ng/ml*h				
geometric mean (geometric coefficient of variation)	23.0 (± 37)	22.4 (± 35)	11.7 (± 61)	11.6 (± 38)

Statistical analyses

Statistical analysis title	Mixed effect model

Statistical analysis description:

Given a clinically relevant difference of 30% in AUC, a within-patient standard deviation of 25%, 80% power and a two-sided significance level of 5%, 14 evaluable patients were required per study group (i.e. with or without esomeprazole) [19]; hence, a total of 28 patients had to be included.

Analyses of AUC 24 and Cmax were performed on logtransformed values, since these parameters were assumed to follow a log-normal distribution [20]. Estimates for the mean differences in (log) AUC 24

Comparison groups	arm 1 v arm 2 v arm 1 v arm 2
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	100
Confidence interval	
level	95 %
sides	2-sided
lower limit	80
upper limit	125
Variability estimate	Standard error of the mean

Secondary: Change in other pharmacokinetic endpoints and toxicity

End point title	Change in other pharmacokinetic endpoints and toxicity
End point description:	
Maximum plasma concentration (Cmax), time until Cmax (Tmax), plasma clearing (Cl) and erlotinib toxicity	
End point type	Secondary
End point timeframe:	
total study period	

End point values	arm 1	arm 2	arm 1	arm 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	15	15	15
Units: ug/ml				
geometric mean (geometric coefficient of variation)	1.85 (± 38)	1.73 (± 21)	0.81 (± 55)	0.82 (± 40)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: total study period: 2 weeks	
Assessment type	Systematic
Dictionary used	
Dictionary name	CTCAE
Dictionary version	5
Reporting groups	
Reporting group title	total cohort

Reporting group description: -

Serious adverse events	total cohort		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 30 (3.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Musculoskeletal and connective tissue disorders			
Spinal fracture			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	total cohort		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 30 (93.33%)		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 30 (20.00%)		
occurrences (all)	12		
Nausea			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	8		
Constipation			

subjects affected / exposed occurrences (all)	5 / 30 (16.67%) 9		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Alopecia subjects affected / exposed occurrences (all)	 23 / 30 (76.67%) 72 12 / 30 (40.00%) 34		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

NA

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32557346