



Clinical trial results:

A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of MK-3102 in 18 and <45 Year-Old Subjects with Type 2 Diabetes Mellitus and Inadequate Glycemic Control

Summary

EudraCT number	2012-004303-12
Trial protocol	RO
Global end of trial date	14 September 2015

Results information

Result version number	v1 (current)
This version publication date	14 September 2016
First version publication date	14 September 2016

Trial information

Trial identification

Sponsor protocol code	MK-3102-028
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01814748
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

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 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 September 2015
Global end of trial reached?	Yes
Global end of trial date	14 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study will examine the safety and efficacy of once-weekly omarigliptin in participants 18 to <45 years of age with Type 2 diabetes mellitus and inadequate glycemic control. The study hypothesis is that treatment with omarigliptin compared with placebo provides greater reduction in hemoglobin A1c (A1C) in participants after 24 weeks.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

The following additional measure defined for this individual study was in place for the protection of trial participants: participants exceeding pre-specified glycemic thresholds after Day 1 of the double-blind treatment period were to have rescue therapy with open-label metformin initiated by the investigator.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 May 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Mexico: 23
Country: Number of subjects enrolled	Romania: 48
Country: Number of subjects enrolled	Russian Federation: 30
Country: Number of subjects enrolled	Serbia: 11
Country: Number of subjects enrolled	South Africa: 14
Country: Number of subjects enrolled	Ukraine: 49
Country: Number of subjects enrolled	United States: 28
Worldwide total number of subjects	203
EEA total number of subjects	48

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)	203
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Eligibility requirements include male and female participants with type 2 diabetes mellitus who were currently not on an antihyperglycemic agent (AHA) for at least the past 12 weeks and has not been treated with omarigliptin at any time prior to study participation.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Omarigliptin 25 mg

Arm description:

Omarigliptin 25 mg, once weekly, for 24 weeks. Open-label metformin daily was to be initiated for participants meeting protocol-specified glycemic criteria, but was otherwise prohibited.

Arm type	Experimental
Investigational medicinal product name	Omarigliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

25 mg administered orally once weekly

Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Open-label metformin (dosed daily according to the country-specific product label) was to be initiated for participants meeting protocol-specified glycemic criteria, but was otherwise prohibited.

Arm title	Placebo
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Arm description:

Placebo to omarigliptin, once weekly, for 24 weeks. Open-label metformin daily was to be initiated for participants meeting protocol-specified glycemic criteria, but was otherwise prohibited.

Arm type	Placebo
Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Open-label metformin (dosed daily according to the country-specific product label) was to be initiated for participants meeting protocol-specified glycemic criteria, but was otherwise prohibited.

Investigational medicinal product name	Placebo to omarigliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Matching placebo to omarigliptin 25 mg administered orally once weekly

Number of subjects in period 1	Omarigliptin 25 mg	Placebo
Started	102	101
Completed	94	94
Not completed	8	7
Consent withdrawn by subject	6	4
Study site terminated by sponsor	1	1
Lost to follow-up	1	2

Baseline characteristics

Reporting groups

Reporting group title	Omarigliptin 25 mg
Reporting group description: Omarigliptin 25 mg, once weekly, for 24 weeks. Open-label metformin daily was to be initiated for participants meeting protocol-specified glycemic criteria, but was otherwise prohibited.	
Reporting group title	Placebo
Reporting group description: Placebo to omarigliptin, once weekly, for 24 weeks. Open-label metformin daily was to be initiated for participants meeting protocol-specified glycemic criteria, but was otherwise prohibited.	

Reporting group values	Omarigliptin 25 mg	Placebo	Total
Number of subjects	102	101	203
Age categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	38.8 ± 4.7	39.5 ± 4.5	-
Gender, Male/Female Units: Participants			
Female	35	41	76
Male	67	60	127
Hemoglobin A1c (A1C) Units: Percent arithmetic mean standard deviation	7.9 ± 0.8	8.1 ± 0.9	-
Fasting plasma glucose (FPG) Units: mg/dL arithmetic mean standard deviation	164 ± 38.9	167.8 ± 40.6	-
2-hour post-meal glucose (2-hr PMG)			
Participants with available data at baseline. Omarigliptin 25 mg, n=98; placebo, n=101			
Units: mg/dL arithmetic mean standard deviation	204.9 ± 55.1	217.3 ± 67.7	-

End points

End points reporting groups

Reporting group title	Omarigliptin 25 mg
Reporting group description: Omarigliptin 25 mg, once weekly, for 24 weeks. Open-label metformin daily was to be initiated for participants meeting protocol-specified glycemic criteria, but was otherwise prohibited.	
Reporting group title	Placebo
Reporting group description: Placebo to omarigliptin, once weekly, for 24 weeks. Open-label metformin daily was to be initiated for participants meeting protocol-specified glycemic criteria, but was otherwise prohibited.	

Primary: Change from baseline in A1C at Week 24

End point title	Change from baseline in A1C at Week 24
End point description: A1C (%) is used to report average blood glucose levels over prolonged periods of time. Analysis population: Full analysis set (FAS) population comprised all participants who received at least one dose of study treatment and had a baseline measurement or a post-randomization measurement for the analysis endpoint. The unexpected absence of a treatment effect in this study led to investigations that included measurement of metformin levels in available samples collected for future research during the study. Of the 92 participants with samples who had not been rescued with metformin, 57% (25/44) in the placebo group and 29% (14/48) in the omarigliptin group had detectable metformin, indicating the use of metformin that was prohibited by the protocol. The use of metformin prohibited by the protocol was without investigator knowledge and is a confounding factor impacting the ability to draw any conclusions regarding the efficacy results from this study.	
End point type	Primary
End point timeframe: Baseline and Week 24	

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	101		
Units: Percent				
least squares mean (confidence interval 95%)	-0.33 (-0.6 to -0.06)	-0.45 (-0.72 to -0.18)		

Statistical analyses

Statistical analysis title	Between group comparison
Comparison groups	Omarigliptin 25 mg v Placebo

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.535 ^[1]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.49

Notes:

[1] - Terms for treatment, time, and the interaction of time by treatment, with the constraint that the mean baseline is the same for all treatment groups. Other method: Constrained longitudinal data analysis (cLDA)

Primary: Percentage of participants who experienced at least one adverse event (AE)

End point title	Percentage of participants who experienced at least one adverse event (AE)
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End point description:

An AE is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure, that occurs during the course of the study. Data presented exclude data following the initiation of glycemic rescue.

Analysis population: All participants treated (APaT) population included all randomized participants who received at least one dose of study medication.

The safety database was analyzed in a standard fashion in the APaT population for all participants who took at least one dose of study medication. This analysis may have been confounded by the use of metformin prohibited by the protocol (see efficacy results description above).

End point type	Primary
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End point timeframe:

Up to Week 27

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	101		
Units: Percentage of participants				
number (not applicable)	39.2	39.6		

Statistical analyses

Statistical analysis title	Between group comparison
Comparison groups	Omarigliptin 25 mg v Placebo

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in percent
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.8
upper limit	13

Primary: Percentage of participants who discontinued study drug due to an AE

End point title	Percentage of participants who discontinued study drug due to an AE
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End point description:

An AE is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure, that occurs during the course of the study. Data presented exclude data following the initiation of glycemic rescue.

Analysis population: APaT population included all randomized participants who received at least one dose of study medication.

The safety database was analyzed in a standard fashion in the APaT population for all participants who took at least one dose of study medication. This analysis may have been confounded by the use of metformin prohibited by the protocol (see efficacy results description above).

End point type	Primary
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End point timeframe:

Up to Week 24

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	101		
Units: Percentage of participants				
number (not applicable)	0	2		

Statistical analyses

Statistical analysis title	Between group comparison
Comparison groups	Omarigliptin 25 mg v Placebo

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other ^[2]
Parameter estimate	Difference in percent
Point estimate	-2
Confidence interval	
level	95 %
sides	1-sided
upper limit	99999

Notes:

[2] - Confidence interval (CI) was not calculated; therefore, 99999 = not calculated.

Secondary: Change from baseline in 2-hr PMG at Week 24

End point title	Change from baseline in 2-hr PMG at Week 24
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End point description:

Blood glucose was measured 120 minutes from start of meal.

Analysis population: FAS population comprised all participants who received at least one dose of study treatment and had a baseline measurement or a post-randomization measurement for the analysis endpoint.

The unexpected absence of a treatment effect in this study led to investigations that included measurement of metformin levels in available samples collected for future research during the study. Of the 92 participants with samples who had not been rescued with metformin, 57% (25/44) in the placebo group and 29% (14/48) in the omarigliptin group had detectable metformin, indicating the use of metformin that was prohibited by the protocol. The use of metformin prohibited by the protocol was without investigator knowledge and is a confounding factor impacting the ability to draw any conclusions regarding the efficacy results from this study.

End point type	Secondary
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End point timeframe:

Baseline and Week 24

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	101		
Units: mg/dL				
least squares mean (confidence interval 95%)	-11.3 (-26.1 to 3.5)	-15.5 (-30.6 to -0.3)		

Statistical analyses

Statistical analysis title	Between group comparison
Comparison groups	Omarigliptin 25 mg v Placebo

Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.685 ^[3]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.1
upper limit	24.4

Notes:

[3] - Terms for treatment, time, and the interaction of time by treatment, with the constraint that the mean baseline is the same for all treatment groups.

Secondary: Change in baseline in FPG at Week 24

End point title	Change in baseline in FPG at Week 24
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End point description:

Blood glucose was measured on a fasting basis.

Analysis population: FAS population comprised all participants who received at least one dose of study treatment and had a baseline measurement or a post-randomization measurement for the analysis endpoint.

The unexpected absence of a treatment effect in this study led to investigations that included measurement of metformin levels in available samples collected for future research during the study. Of the 92 participants with samples who had not been rescued with metformin, 57% (25/44) in the placebo group and 29% (14/48) in the omarigliptin group had detectable metformin, indicating the use of metformin that was prohibited by the protocol. The use of metformin prohibited by the protocol was without investigator knowledge and is a confounding factor impacting the ability to draw any conclusions regarding the efficacy results from this study.

End point type	Secondary
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End point timeframe:

Baseline and Week 24

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	101		
Units: mg/dL				
least squares mean (confidence interval 95%)	-5 (-14.6 to 4.6)	-1.3 (-11.2 to 8.5)		

Statistical analyses

Statistical analysis title	Between group comparison
Comparison groups	Omarigliptin 25 mg v Placebo

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.586 ^[4]
Method	Constrained longitudinal data analysis
Parameter estimate	Difference in least squares means
Point estimate	-3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.1
upper limit	9.7

Notes:

[4] - Terms for treatment, time, and the interaction of time by treatment, with the constraint that the mean baseline is the same for all treatment groups.

Secondary: Percentage of participants attaining A1C glycemic goals of <7.0% at Week 24

End point title	Percentage of participants attaining A1C glycemic goals of <7.0% at Week 24
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End point description:

Percentage of participants was estimated using standard multiple imputation techniques (cLDA model). Within-group CIs were calculated via the Wilson score method. FAS population comprised all participants who received at least one dose of study treatment and had a baseline measurement or a post-randomization measurement for the analysis endpoint. The unexpected absence of a treatment effect in this study led to investigations that included measurement of metformin levels in available samples collected for future research during the study. Of the 92 participants with samples who had not been rescued with metformin, 57% (25/44) in the placebo group and 29% (14/48) in the omarigliptin group had detectable metformin, indicating the use of metformin that was prohibited by the protocol. The use of metformin prohibited by the protocol was without investigator knowledge and is a confounding factor impacting the ability to draw any conclusions regarding the efficacy results from this study.

End point type	Secondary
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End point timeframe:

Week 24

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	101		
Units: Percentage of participants				
number (confidence interval 95%)	33.5 (24.7 to 43.7)	34 (25.1 to 44.1)		

Statistical analyses

Statistical analysis title	Between group comparison
Comparison groups	Omarigliptin 25 mg v Placebo

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other
Method	Miettinen and Nurminen
Parameter estimate	Between-group rate difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14
upper limit	13.1

Secondary: Percentage of participants attaining A1C glycemic goals of <6.5% at Week 24

End point title	Percentage of participants attaining A1C glycemic goals of <6.5% at Week 24
End point description:	
<p>Percentage of participants was estimated using standard multiple imputation techniques (cLDA model). Within-group CIs were calculated via the Wilson score method. FAS population comprised all participants who received at least one dose of study treatment and had a baseline measurement or a post-randomization measurement for the analysis endpoint. The unexpected absence of a treatment effect in this study led to investigations that included measurement of metformin levels in available samples collected for future research during the study. Of the 92 participants with samples who had not been rescued with metformin, 57% (25/44) in the placebo group and 29% (14/48) in the omarigliptin group had detectable metformin, indicating the use of metformin that was prohibited by the protocol. The use of metformin prohibited by the protocol was without investigator knowledge and is a confounding factor impacting the ability to draw any conclusions regarding the efficacy results from this study.</p>	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	101		
Units: Percentage of participants				
number (confidence interval 95%)	21.7 (14.5 to 31.1)	17.6 (11.3 to 26.5)		

Statistical analyses

Statistical analysis title	Between group comparison
Comparison groups	Omarigliptin 25 mg v Placebo

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other
Method	Miettinen and Nurminen
Parameter estimate	Between-group rate difference
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.4
upper limit	15.5

Secondary: Percentage of participants who required glycemic rescue by Week 24

End point title	Percentage of participants who required glycemic rescue by Week 24
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End point description:

Participants exceeding pre-specified glycemic thresholds after starting the double-blind treatment period may have received rescue therapy (per protocol) with open-label metformin initiated by the investigator.

Analysis population: all randomized participants.

This analysis may have been confounded by the use of metformin prohibited by the protocol (see efficacy results description above).

End point type	Secondary
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End point timeframe:

Up to Week 24

End point values	Omarigliptin 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	101		
Units: Percentage of participants				
number (not applicable)	10.8	12.9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 27 weeks; Serious adverse events (SAEs) were collected up to 24 weeks during treatment + 3 week follow-up, non-serious adverse events (NSAEs) were collected up to 24 weeks during treatment

Adverse event reporting additional description:

SAEs include data after glycemic rescue; NSAEs exclude data after glycemic rescue. Investigations performed by the Sponsor revealed that many participants had used a prohibited antihyperglycemic agent—metformin (i.e., not as rescue medication; see efficacy results description above).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo to omarigliptin, once weekly, for 24 weeks. Open-label metformin daily was to be initiated for participants meeting protocol-specified glycemic criteria, but was otherwise prohibited.

Reporting group title	Omarigliptin 25 mg
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Reporting group description:

Omarigliptin 25 mg, once weekly, for 24 weeks. Open-label metformin daily was to be initiated for participants meeting protocol-specified glycemic criteria, but was otherwise prohibited.

Serious adverse events	Placebo	Omarigliptin 25 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 101 (2.97%)	1 / 102 (0.98%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 101 (0.99%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvovaginal candidiasis			

subjects affected / exposed	1 / 101 (0.99%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 101 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Omarigliptin 25 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 101 (6.93%)	10 / 102 (9.80%)	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 101 (5.94%)	6 / 102 (5.88%)	
occurrences (all)	6	6	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 101 (1.98%)	6 / 102 (5.88%)	
occurrences (all)	2	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 August 2013	Amendment 1: primary reason was to add amylase and lipase to the chemistry panel.

Notes:

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.

Investigations indicate that the presence of metformin in future biomedical research (FBR) samples from non-rescued participants was due to participant self-administration of metformin outside of the protocol and without investigator knowledge.

Notes: