ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: January 17, 2018

ClinicalTrials.gov ID: NCT00677365

Study Identification

Unique Protocol ID:	Mpex-204
Brief Title:	Safety, Tolerability and Efficacy of MP-376 Given for 28 Days to Cystic Fibrosis (CF) Patients
Official Title:	Phase II, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Study to Evaluate the Safety, Tolerability and Efficacy of Three Dosage Regimens of MP-376 Solution for Inhalation Given for 28 Days to Stable CF Patients
Secondary IDs:	2008-001728-30 [EudraCT Number]

Study Status

Record Verification:	January 2018
Overall Status:	Completed
Study Start:	June 2008 []
Primary Completion:	June 2009 [Actual]
Study Completion:	June 2009 [Actual]

Sponsor/Collaborators

Sponsor:	Horizon Pharma USA, Inc.
Responsible Party:	Sponsor
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	

Unapproved/Uncleared Device:	No
U.S. FDA IND/IDE:	Yes
IND/IDE Information:	FDA Center: CDER IND/IDE Number: 75,290 Serial Number: 0012 Has Expanded Access No
Human Subjects Review:	Board Status: Approved Board Name: Western Institutional Review Board (WIRB) Board Affiliation: Western Institutional Review Board (WIRB) Phone: 360-252-2500 Email: Address: 3535 Seventh Avenue Olympia, WA 98502-5010 Contact: Theodore D. Schultz, JD
Data Monitoring:	Yes
FDA Regulated Intervention:	Yes
Section 801 Clinical Trial:	No

Study Description

Brief Summary:	Patients with cystic fibrosis (CF) suffer from chronic infections of the lower respiratory tract that can be caused by one or multiple bacteria, including Pseudomonas aeruginosa, which has been particularly problematic to eradicate and been implicated as the major cause of morbidity and mortality in CF patients. Aerosol delivery of antibiotics directly to the lung increases the local concentrations of antibiotic at the site of infection resulting in improved antimicrobial effects compared to systemic administration. Bacterial resistance to current aerosol antibiotic treatments indicate a need for improved therapies to treat CF patients with pulmonary infections caused by multi-drug resistant Pseudomonas aeruginosa and other bacteria. High concentrations of MP-376 delivered directly to the lung are projected to have antimicrobial effects on even the most resistant organisms.
Detailed Description:	This trial will be a double-blind, placebo-controlled study to evaluate the safety, tolerability and efficacy of levofloxacin administered as MP-376 of three dosage regimens given for 28 days by the aerosol route to CF patients.

Conditions

Conditions:	Cystic Fibrosis (CF)
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Interventional Study Model:	Parallel Assignment
Number of Arms:	4
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Allocation:	Randomized
Enrollment:	151 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Placebo Comparator: Placebo Placebo inhaled either once or twice daily via the PARI eFlow nebulizer for 28 days	Drug: Placebo same frequency as study drug using the same nebulizer
Experimental: MP-376 120 mg QD MP-376 120 mg inhaled Once Daily (QD) via the PARI eFlow nebulizer for 28 days	Drug: MP-376 3 dose regimens of MP-376 administered twice daily (BID) or once daily (QD) for 28 days Other Names: • Levofloxacin Inhalation Solution • Aeroquin
Experimental: MP-376 240 mg QD MP-376 240 mg inhaled QD bia the PARI eFlow nebulizer for 28 days	Drug: MP-376 3 dose regimens of MP-376 administered twice daily (BID) or once daily (QD) for 28 days Other Names: • Levofloxacin Inhalation Solution • Aeroquin
Experimental: MP-376 240 mg BID MP-376 240 mg inhaled twice daily (BID) via the PARI eFlow nebulizer for 28 days	Drug: MP-376 3 dose regimens of MP-376 administered twice daily (BID) or once daily (QD) for 28 days Other Names: • Levofloxacin Inhalation Solution • Aeroquin

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 16 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria (selected):

- > 16 years of age
- Confirmed Diagnosis of Cystic Fibrosis
- Positive sputum culture for P. aeruginosa within the past 18 months
- Patients are able to elicit a forced expiratory volume in 1 second (FEV1) >/= 25% but </= 85% of predicted value at screening
- Have received at least 3 courses of inhaled antimicrobials over the preceding 12 months
- Clinically stable with no changes in health status within the last 30 days
- Able to reproducibly produce sputum and perform spirometry

Exclusion Criteria (selected):

- Use of any nebulized or systemic antibiotics within 30 days prior to baseline
- History of hypersensitivity to fluoroquinolones or intolerance with aerosol medication
- Evidence of acute upper within 10 days or lower respiratory infections within 30 days prior to dosing
- Creatine clearance < 50mg/ml, aspartate transaminase (AST), alanine transaminase (ALT) or total bilirubin >/= 3 x upper limit of normal (ULN) at Screening

Contacts/Locations

Central Contact Person: Jeff Nieves, PharmD
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Central Contact Backup:

Study Officials: Douglas J Conrad, M.D.
Study Principal Investigator
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Locations: United States, South Carolina

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Los Angeles, California, United States, 90033

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Oklahoma City, Oklahoma, United States, 73112

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Columbia, South Carolina, United States, 29203

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Munchen, Germany

Gerlingen, Germany

Kiel, Germany

Essen, Germany

Frankfurt, Germany

Gieben, Germany

Netherlands
Rotterdam, Netherlands

Groesbeek, Netherlands

Amsterdam, Netherlands

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Study Results

Participant Flow

Reporting Groups

	Description
Placebo	Placebo Group
MP-376 120 mg QD	MP-376 120 mg Once Daily (QD) Group
MP-376 240 mg QD	MP-376 240 mg Once Daily (QD) Group
MP-376 240 mg BID	MP-376 240 mg Twice Daily (BID) Group

Overall Study

	Placebo	MP-376 120 mg QD	MP-376 240 mg QD	MP-376 240 mg BID
Started	37	38	37	39
Completed	35	37	35	36
Not Completed	2	1	2	3
Adverse Event	2	1	1	2
Withdrawal by Subject	0	0	1	0
Other reason	0	0	0	1

Baseline Characteristics

Reporting Groups

	Description
Placebo	Placebo Group
MP-376 120 mg QD	MP-376 120 mg Once Daily (QD) Group
MP-376 240 mg QD	MP-376 240 mg Once Daily (QD) Group
MP-376 240 mg BID	MP-376 240 mg Twice Daily (BID) Group

Baseline Measures

		Placebo	MP-376 120 mg QD	MP-376 240 mg QD	MP-376 240 mg BID	Total
Overall Number of Participants		37	38	37	39	151
Age, Continuous Mean (Standard Deviation) Unit of measure: years	Number Analyzed	37 participants	38 participants	37 participants	39 participants	151 participants
		30.1 (9.94)	28.0 (6.86)	27.5 (9.05)	29.2 (9.98)	28.7 (9.02)
Sex: Female, Male Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	37 participants	38 participants	37 participants	39 participants	151 participants
	Female	18 48.65%	18 47.37%	16 43.24%	14 35.9%	66 43.71%
	Male	19 51.35%	20 52.63%	21 56.76%	25 64.1%	85 56.29%
Region of Enrollment Measure Type: Number Unit of measure: Participants	Number Analyzed	37 participants	38 participants	37 participants	39 participants	151 participants
United States		30	32	30	32	124
Europe		7	6	7	7	27

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Change in P. Aeruginosa Density

Measure Description	Patients were required to cough deeply and then spit sputum into a sterile container. The bacteria contained in the sputum sample was incubated in a laboratory and the number of P. aeruginosa colony forming units per gram of sputum (CFU/g) was determined. The difference in CFUs/g were then compared from baseline to the conclusion of the 28 day treatment period
Time Frame	from baseline to end of treatment (28 days)

Analysis Population Description

Modified Intent-to-Treat (MITT; patients who received at least one dose of study drug)

Reporting Groups

	Description
Placebo	Placebo Group
MP-376 120 mg QD	MP-376 120 mg Once Daily (QD) Group
MP-376 240 mg QD	MP-376 240 mg Once Daily (QD) Group
MP-376 240 mg BID	MP-376 240 mg Twice Daily (BID) Group

Measured Values

	Placebo	MP-376 120 mg QD	MP-376 240 mg QD	MP-376 240 mg BID
Overall Number of Participants Analyzed	37	38	37	39
Change in P. Aeruginosa Density Least Squares Mean (Standard Error) Unit of measure: log10 CFU/g sputum	0.23 (0.220)	-0.31 (0.227)	-0.31 (0.220)	-0.73 (0.222)

Statistical Analysis 1 for Change in P. Aeruginosa Density

Statistical Analysis Overview	Comparison Group Selection	Placebo, MP-376 240 mg BID
	Comments	LS Mean Difference
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0014
	Comments	Repeated Measure Model
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.96
	Confidence Interval	(2-Sided) 95% -1.54 to -0.38
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Time to Administration of Other Anti-pseudomonal Antimicrobials
Measure Description	Time to administration of other anti-pseudomonal antimicrobials in patients with at least one of the following: decreased exercise tolerance, increased cough, increased sputum/chest congestion, or decreased appetite; 25th percentile data reported
Time Frame	from baseline until final study visit (up to 56 days)

Analysis Population Description

MITT

Reporting Groups

	Description
Placebo	Placebo Group
MP-376 120 mg QD	MP-376 120 mg Once Daily (QD) Group
MP-376 240 mg QD	MP-376 240 mg Once Daily (QD) Group
MP-376 240 mg BID	MP-376 240 mg Twice Daily (BID) Group

Measured Values

	Placebo	MP-376 120 mg QD	MP-376 240 mg QD	MP-376 240 mg BID
Overall Number of Participants Analyzed	37	38	37	39
Time to Administration of Other Anti-pseudomonal Antimicrobials Mean (95% Confidence Interval) Unit of measure: days	31 (29 to 43)	NA (32 to NA) [1]	56 (43 to NA) [2]	59 (57 to NA) [2]

[1] Not available; 25th percentile was not reached within the 56-day study duration

[2] Not available; The upper range of the confidence interval exceeds the 56-day study duration

Statistical Analysis 1 for Time to Administration of Other Anti-pseudomonal Antimicrobials

Statistical Analysis Overview	Comparison Group Selection	Placebo, MP-376 240 mg BID
	Comments	Hazard Ratio for need of anti-pseudomonal antimicrobials; Estimates are obtained from a Cox proportional hazards regression model including terms for treatment, region, baseline P.aeruginosa density (log10), highest baseline MIC of levofloxacin against P. aeruginosa (log2), and baseline percent predicted FEV1 (quartiles)
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0007
	Comments	[Not specified]
	Method	Regression, Cox
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.21
	Confidence Interval	(2-Sided) 95% 0.09 to 0.52
	Estimation Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Percent Change in Forced Expiratory Volume in 1 Second (FEV1)
Measure Description	Percent change in the amount of air the patient could exhale in 1 second
Time Frame	from baseline to end of the 28-day treatment period (28 days)

Analysis Population Description
MITT

Reporting Groups

	Description
Placebo	Placebo Group
MP-376 120 mg QD	MP-376 120 mg Once Daily (QD) Group
MP-376 240 mg QD	MP-376 240 mg Once Daily (QD) Group
MP-376 240 mg BID	MP-376 240 mg Twice Daily (BID) Group

Measured Values

	Placebo	MP-376 120 mg QD	MP-376 240 mg QD	MP-376 240 mg BID
Overall Number of Participants Analyzed	37	38	37	39
Percent Change in Forced Expiratory Volume in 1 Second (FEV1) Least Squares Mean (Standard Error) Unit of measure: Percent change	-2.36 (2.085)	1.93 (2.114)	2.56 (2.077)	6.25 (2.081)

Statistical Analysis 1 for Percent Change in Forced Expiratory Volume in 1 Second (FEV1)

Statistical Analysis Overview	Comparison Group Selection	Placebo, MP-376 240 mg BID
	Comments	LS Mean Difference Between MP-376 240 mg and Placebo groups
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0026
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	8.61
	Confidence Interval	(2-Sided) 95% 3.05 to 14.17
	Estimation Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Change in FEV1 Percent Predicted
Measure Description	Change in the predicted percent of air the patient could exhale in one second
Time Frame	from baseline to the end of the treatment 28-day treatment period (28 days)

Analysis Population Description
MITT

Reporting Groups

	Description
Placebo	Placebo Group
MP-376 120 mg QD	MP-376 120 mg Once Daily (QD) Group
MP-376 240 mg QD	MP-376 240 mg Once Daily (QD) Group
MP-376 240 mg BID	MP-376 240 mg Twice Daily (BID) Group

Measured Values

	Placebo	MP-376 120 mg QD	MP-376 240 mg QD	MP-376 240 mg BID
Overall Number of Participants Analyzed	37	38	37	39
Change in FEV1 Percent Predicted Least Squares Mean (Standard Error) Unit of measure: Percent	-2.39 (2.370)	1.96 (2.402)	3.10 (2.361)	8.55 (2.358)

Statistical Analysis 1 for Change in FEV1 Percent Predicted

Statistical Analysis Overview	Comparison Group Selection	Placebo, MP-376 240 mg BID
	Comments	LS Mean Difference Between Placebo and MP-376 240 mg BID groups
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0008
	Comments	[Not specified]
	Method	Mixed Models Analysis
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	10.94
	Confidence Interval	(2-Sided) 95% 4.63 to 17.25
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Changes in Respiratory Domain Scores of Cystic Fibrosis Questionnaire - Revised (CFQ-R)
Measure Description	Change in the score from 0 to 100 that a patient reports for their respiratory symptoms in the CFQ-R. An increase in score illustrates an improvement in symptoms. An increase of 4 or more is considered clinically significant
Time Frame	from baseline to the end of the 28-day treatment period (28 days)

Analysis Population Description
MITT

Reporting Groups

	Description
Placebo	Placebo Group
MP-376 120 mg QD	MP-376 120 mg Once Daily (QD) Group
MP-376 240 mg QD	MP-376 240 mg Once Daily (QD) Group
MP-376 240 mg BID	MP-376 240 mg Twice Daily (BID) Group

Measured Values

	Placebo	MP-376 120 mg QD	MP-376 240 mg QD	MP-376 240 mg BID
Overall Number of Participants Analyzed	37	38	37	39
Changes in Respiratory Domain Scores of Cystic Fibrosis Questionnaire - Revised (CFQ-R) Least Squares Mean (Standard Error) Unit of measure: units on a scale	-0.44 (2.715)	2.00 (2.728)	0.31 (2.689)	4.06 (2.690)

Statistical Analysis 1 for Changes in Respiratory Domain Scores of Cystic Fibrosis Questionnaire - Revised (CFQ-R)

Statistical Analysis Overview	Comparison Group Selection	Placebo, MP-376 240 mg BID
	Comments	LS Mean Difference from MP-376 240 mg BID to placebo groups
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2174
	Comments	[Not specified]
	Method	Mixed Models Analysis

	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	4.50
	Confidence Interval	(2-Sided) 95% -2.68 to 11.67
	Estimation Comments	[Not specified]

6. Secondary Outcome Measure:

Measure Title	Changes in Susceptability Patterns of Isolated Organisms
Measure Description	All isolates of P. aeruginosa cultures grown from patient sputum samples were evaluated to see whether the minimum concentration of levofloxacin needed to inhibit growth of the bacteria (i.e., minimum inhibitory concentration; MIC) had increased; 2. The MIC50 and MIC90 values were calculated as the 50th percentile value and the 90th percentile value, respectively. Note that percentile values between dilution values were rounded up to the nearest dilution value
Time Frame	from baseline until the end of the 28-day treatment period (28 days)

Analysis Population Description
MITT

Reporting Groups

	Description
Placebo	Placebo Group
MP-376 120 mg QD	MP-376 120 mg Once Daily (QD) Group
MP-376 240 mg QD	MP-376 240 mg Once Daily (QD) Group
MP-376 240 mg BID	MP-376 240 mg Twice Daily (BID) Group

Measured Values

	Placebo	MP-376 120 mg QD	MP-376 240 mg QD	MP-376 240 mg BID
Overall Number of Participants Analyzed	37	38	37	39
Overall Number of Units Analyzed Type of Units Analyzed: Isolates	140	152	148	152
Changes in Susceptability Patterns of Isolated Organisms Measure Type: Number Unit of measure: ug/mL				

	Placebo	MP-376 120 mg QD	MP-376 240 mg QD	MP-376 240 mg BID
Baseline Minimum Inhibitory Concentration (MIC)50	4	4	4	4
Day 28 MIC for 50% (MIC50)	4	4	4	4
Baseline MIC for 90% (MIC90)	16	32	16	16
Day 28 MIC90	8	16	16	32

Reported Adverse Events

Time Frame	[Not specified]
Adverse Event Reporting Description	[Not specified]

Reporting Groups

	Description
Placebo	Placebo Group
MP-376 120 mg QD	MP-376 120 mg Once Daily (QD) Group
MP-376 240 mg QD	MP-376 240 mg Once Daily (QD) Group
MP-376 240 mg BID	MP-376 240 mg Twice Daily (BID) Group

All-Cause Mortality

	Placebo		MP-376 120 mg QD		MP-376 240 mg QD		MP-376 240 mg BID	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total All-Cause Mortality	/		/		/		/	

Serious Adverse Events

	Placebo		MP-376 120 mg QD		MP-376 240 mg QD		MP-376 240 mg BID	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	4/37 (10.81%)		1/38 (2.63%)		4/37 (10.81%)		4/39 (10.26%)	
General disorders								
Disease progression [A] [1] †	3/37 (8.11%)	3	0/38 (0%)	0	4/37 (10.81%)	4	3/39 (7.69%)	3
Infections and infestations								
Appendicitis [A] †	0/37 (0%)	0	1/38 (2.63%)	1	0/37 (0%)	0	1/39 (2.56%)	1
Bronchitis [A] †	1/37 (2.7%)	1	0/38 (0%)	0	0/37 (0%)	0	0/39 (0%)	0
Pneumonia [A] †	0/37 (0%)	0	0/38 (0%)	0	0/37 (0%)	0	1/39 (2.56%)	1
Metabolism and nutrition disorders								
Diabetes Mellitus [A] †	1/37 (2.7%)	1	0/38 (0%)	0	0/37 (0%)	0	0/39 (0%)	0

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA

[1] Pulmonary exacerbation

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Placebo		MP-376 120 mg QD		MP-376 240 mg QD		MP-376 240 mg BID	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	28/37 (75.68%)		33/38 (86.84%)		32/37 (86.49%)		33/39 (84.62%)	
Gastrointestinal disorders								
Diarrhea [A] †	2/37 (5.41%)	2	2/38 (5.26%)	2	4/37 (10.81%)	4	1/39 (2.56%)	1

	Placebo		MP-376 120 mg QD		MP-376 240 mg QD		MP-376 240 mg BID	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Nausea [A] †	1/37 (2.7%)	1	3/38 (7.89%)	3	1/37 (2.7%)	1	3/39 (7.69%)	3
Vomiting [A] †	1/37 (2.7%)	1	2/38 (5.26%)	2	2/37 (5.41%)	2	2/39 (5.13%)	2
General disorders								
Chest Discomfort [A] †	3/37 (8.11%)	3	0/38 (0%)	0	2/37 (5.41%)	2	4/39 (10.26%)	5
Disease progression [A] [1] †	10/37 (27.03%)	12	4/38 (10.53%)	4	8/37 (21.62%)	9	7/39 (17.95%)	7
Pyrexia [A] †	3/37 (8.11%)	3	0/38 (0%)	0	2/37 (5.41%)	2	6/39 (15.38%)	6
Infections and infestations								
Nasopharyngitis [A] †	3/37 (8.11%)	3	1/38 (2.63%)	1	3/37 (8.11%)	4	3/39 (7.69%)	3
Nervous system disorders								
Dysgeusia [A] [2] †	1/37 (2.7%)	1	14/38 (36.84%)	15	18/37 (48.65%)	19	13/39 (33.33%)	14
Headache [A] †	0/37 (0%)	0	7/38 (18.42%)	8	2/37 (5.41%)	2	4/39 (10.26%)	4
Respiratory, thoracic and mediastinal disorders								
Cough [A] †	6/37 (16.22%)	7	9/38 (23.68%)	9	10/37 (27.03%)	12	10/39 (25.64%)	11
Hemoptysis [A] †	7/37 (18.92%)	9	3/38 (7.89%)	3	5/37 (13.51%)	6	2/39 (5.13%)	2
Pharyngeal pain [A] †	1/37 (2.7%)	1	2/38 (5.26%)	2	2/37 (5.41%)	2	3/39 (7.69%)	3
Productive cough [A] †	4/37 (10.81%)	4	3/38 (7.89%)	3	3/37 (8.11%)	3	2/39 (5.13%)	2

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA

[1] Pulmonary exacerbation

[2] Taste complaint

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There is NOT an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Results Point of Contact:

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