Safety Reporting Guide

Purpose: This document serves as a guide for health care professionals who have patients enrolled in this study to comply with the reporting of patient safety events.

This study collects information about women who are pregnant and have been exposed to Palynziq, as well as information on their infants. Information about specific safety events will also be collected during the pregnancy. As an HCP with a patient enrolled in this study, you will need to provide information on these events and pregnancies within 1 business day from when you are made aware. You will complete a set of forms which will assist you in the collection and reporting of this required information. The information below is designed to facilitate reporting and provide a more robust clinical picture of the safety event. Also included below are field by field completion instructions for the safety event report forms.

Definitions:

Adverse Event (AE) - is any untoward medical occurrence in a subject temporally associated with the use of medicinal product, whether or not considered related to the treatment with Pegvaliase.

Adverse Drug Reaction (ADR)/ Adverse Reaction (AR) - Any untoward medical occurrence in a subject administered medicinal product that is judged by the reporting HCP (or Sponsor) as having a reasonable causal relationship to Pegvaliase

- Pre-existing medical conditions judged by the HCP to have worsened in severity or frequency or changed in character during the study and assessed as related to Pegvaliase

Serious Adverse Event (SAE) - An SAE is any untoward medical occurrence that meets 1 or more of the following criteria:

- Is fatal
- Is life-threatening (Note: life-threatening refers to an event that places the subject at immediate risk of death. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death).
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability or incapacity
- Is a Congenital Malformation (CM) or birth defect in the child or fetus of a patient receiving the medication under study.
- Is an important medical event or reaction – that, based on medical judgment, may jeopardize the patient or require intervention to prevent one of the above consequences (e.g., anaphylaxis).

Health Care Professional (HCP) – physician, osteopath, registered nurse, nurse practitioner, dentist

Clinically Significant Laboratory Abnormalities: Laboratory values are assessed by the subject's HCP. If a lab abnormality is assessed as clinically significant in accordance with the guidelines below, the HCP will then assess if the event meets the reporting criteria for this program. If yes, then the HCP should

complete the Safety Event Report form and submit to Syneos Health, the Contract Research Organization (CRO) supporting BioMarin with the study.

- A clinically significant laboratory abnormality confirmed by repeat test per standard of care is defined as any one or more of the following:
  - accompanied by clinical symptoms
  - change in medication therapy
  - abnormality suggests disease or organ toxicity

Safety events required to be reported under this study:

Maternal Safety Events:

All Serious Adverse Events

All ADRs, except grade 1 and 2 injection site reactions

Anaphylaxis

Acute Systemic Hypersensitivity Reaction

Hypophenylalanemia (defined as 2 consecutive measures ≤ 30µmol/L)

Infant Safety Events:

Congenital Anomaly/Birth defect

All Serious Adverse Events

Hypersensitivity reaction to Pegvaliase via breast milk

Failure to Thrive

Small Gestational Age

Skin reactions continuing without improvement for > 14 days

Anaphylactic reactions

Angioedema

Serum Sickness

Excluded from Reporting:

Non serious adverse events assessed as not related to Pegvaliase

Hospitalization for routine childbirth, including planned C-section

Planned hospitalizations

Injection site reactions assessed as Grade 1 or 2

Assessments made by the reporting HCP

Event term – An event term should be a medical diagnosis whenever possible. If only signs/symptoms are available when information is first received, use your clinical judgement and enter the single most clinically significant sign or symptom as a temporary event term. Include all the other signs and symptoms in the event description field. When you receive additional information, update the previously submitted form, updating the event term to a diagnosis. Use a single line to strike through the previous information. Record the new information, initial and date the entry, then submit the updated form to Syneos Health.

Seriousness - If the event meets any of the seriousness criteria above, select all the serious criteria that apply.

Severity – Select the severity of the event

CTCAE grading criteria – Common Terminology Criteria for Adverse Events (CTCAE) (cancer.gov) Please Click the link above to access the online version of this document.

This is an example from the CTCAE Grading document.

Injection site reaction	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection.					
Navigational Note: -					

The event term is in the left column. The information in the columns marked Grade 1 through Grade 5 is meant to represent the clinical manifestation and/or intervention of the event. Important notes for using the guide: the semi colon (;) represents the "or" function. The hyphen in a column indicates that grade is not applicable to the event. If an event term cannot be found in the CTCAE Grading document, the general grading table found at the beginning of the CTCAE document can be used.

Causality – This is a mandatory field. As the reporting HCP, it is your responsibility to assess each event and determine a causality of the event in relation to treatment with Pegvaliase. An assessment of "Related" indicates that there are facts, evidence and/or arguments to suggest a causal relationship or that such a relationship could not be ruled out. The HCP may change her/his opinion of causality if additional information is received after the initial report.

Outcome - Indicate the outcome of the adverse event.

Recovered/Resolved: Event has resolved and the subject returned to his/her health status prior to the event. Enter the date the event resolved.

Recovered/Resolved with Sequelae: Refers to an event where the acute phase has resolved but residual signs or symptoms are present and establish a new baseline health status, as the signs/symptoms are not expected to fully resolve. Enter the date the event resolved. An example of this could be an event of Tympanic membrane perforation that heals, but the patient has minor hearing loss afterward. The perforation healed, but the sequelae is the minor hearing loss.

Not Recovered/Not Resolved: Event continues without improvement

Recovering/Resolving: Event is improving, but not yet fully resolved.

Fatal: Patient died as a result of the reported AE. Enter the date of death and if Autopsy was performed

Lost to Follow up/ Outcome unknown.

Event Description: this is important information, as the details provided will allow the Sponsor to gain an understanding of the clinical presentation and course of the event. It should be a short summary providing the pertinent details of the clinical course, diagnostic results, treatment and response. Consider including relevant medical history, concomitant medications and/or other factors that could have contributed to the event. Think of this description as a summary you would provide a colleague covering for you.

Once you complete the report and submit it, you may receive requests for additional information. If you have the information available, please reply as quickly as possible to the request. If the information is not available, return the request, documenting you do not have the requested information.

The following is a list of forms for reporting pregnancy and safety event information. Completion instructions for each of these forms follows.

Pregnancy Report form

Pregnancy Outcome Form

Safety Event Report form

INSTRUCTIONS ONLY – DO NOT COMPLETE

Pregnancy Report Form

COMPLETION INSTRUCTIONS

165-504

Complete form, print, sign and Fax/Email the Pregnancy Form to Syneos Health @ +1 800-800-1052 or email to palynziqpregnancystudy@syneoshealth.com within 1 business day of learning of the event.

The initial report of pregnancy will be captured on the Pregnancy Report Form and the Pregnancy Outcome report form will be used to report the outcome of the pregnancy

Reporting Initial Information & Correcting Erroneous Information

When reporting initial information on patient pregnancy participating in the 165-504 registry, use the study specific pregnancy report form. Do not leave any section blank, if the information is not available, please note in the appropriate sections. If after sending the report, updates or corrections are required, draw a single line through the incorrect information on the original form, then write in the new information, date and initial this new entry. **Please indicate on the fax coversheet, this report contains new information.**

Reporting Follow-Up Information during the pregnancy

As soon as missing information or additional information becomes available, as follow the directions in the paragraph. **Once the pregnancy outcome becomes available, it should be reported on the study Pregnancy Outcome Report Form.**

Signatures

If the reporting Physician is completing the form, the physician should sign each iteration of the Safety Event Report Form that is sent to Syneos. If the CRP or Syneos associate is filling out the form during contact with the HCP, Syneos will enter the HCP name and title and complete the secondary signature line and enter Syneos Health in the title field. Please note for follow up reports, the reporting physician may initial and date behind their original signature for each subsequent updated report. This same convention also applies to the CRP/Syneos associate signatures.

Please contact Syneos for any questions regarding adverse event collection or reporting at **+1 833-672-2203.**

Pregnancy Form Instructions by Section

BMN 165-504	
General Information	
Patient ID	Enter the full subject number
Date of Birth	Enter the subject's Date of Birth using a DD-MMM-YYYY format (ex, 01-May-2001) reporting in accordance with local privacy rules
Participating in 165-501?	Check the appropriate box
Reporter Information	
Name of Reporter	Enter name of reporter
HCP	Check the appropriate box
HCP Type	Check the appropriate box
Specialty	Enter practice specialty if appropriate
Country	Enter country
email	Enter email address
Phone	Enter telephone number
Product Information	
Product	This field will be pre-populated
Dose	Please provide the dose that the subject received was receiving
Frequency	Please provide the frequency of dose
Route	This field will be pre-populated
Date of first dose	Please provide the date of the mother's first dose
Stop Date of Palynziq	Enter the date treatment with Palynziq was stopped if appropriate
Most recent dose prior to LMP	Enter the date of mother's most recent dose prior to pregnancy
Lot#/Expiration Date	This information can be located on the label on the drug kit. Enter NA if not available
Pregnancy Information	
Report of Current Pregnancy Is	Please check the appropriate box indicating if the pregnancy meets the definition for Prospective or Retrospective.
1st Day of LMP	Enter the date of the first day of the patient's last menstrual period
Estimated Due Date	Enter the estimated date of delivery
Pregnancy Ongoing	Please Check the appropriate box.
Pregnancy Type	Check the appropriate box. If a multiple pregnancy, enter the number fetus

Obstetrical History (exclude current pregnancy)	
Total Number of previous Pregnancy	Enter the number of previous pregnancies by in the appropriate column to indicate if the pregnancy occurred while the patient was receiving Palynziq or not.
Number of full-term live births	List medications that the subject was taking at the time the adverse event occurred, including any pre-medication the subject received prior to the biospecimen collection procedure (if applicable). Please do not include treatment medication.
Number of Pre-term live births	List any medication suspected by the investigator as having caused or contributed to the event. Provide indication, dosing information, and dates for all suspect medications.
Number of Spontaneous Abortion/Miscarriage	Identify any other possible causes that may have caused or contributed to the event (e.g., underlying disease, new medical conditions, etc.)
Number of Therapeutic Abortion	List the results for any relevant laboratory tests performed in conjunction with the event. Please summarize all labs. Do not attach lab reports unless requested.
Number of Ectopic Pregnancies	List all other medically relevant conditions/pre-existing medical conditions the subject had at the time of the onset of the event. Relevant family history or other outstanding risk factors (smoking, alcohol, etc.)
Number of Molar Pregnancies	Enter the appropriate number
Number of Stillbirth and Gestational week in weeks	Enter the appropriate number
Infants with Congenital Anomalies	Enter the appropriate number
Provide infant gender and congenital anomalies observed	Provide requested information for each infant
Family History of Congenital Anomalies	
Maternal family history of congenital anomalies	Check appropriate box, if yes, enter the type(s) of congenital anomalies.
Paternal family history of congenital anomalies	Check appropriate box, if yes, enter the type(s) of congenital anomalies.
Concurrent/Medical History	
Enter medical conditions that are concurrent or historical	Enter conditions and start dates and if appropriate stop dates.
Concomitant Medications	
Medication Name	Enter medications taken within 30 days of LMP and/or during the pregnancy. Enter the requested information in each column and check the box in the Stop Date/ Ongoing column to indicate the medication therapy is ongoing during the pregnancy.

Other Substance Exposure	
Substance	Enter the requested information in each column and check the box in the Stop Date/ Ongoing column to indicate the use is ongoing during the pregnancy.
Signature Section	
HCP Name, Date	Please include the reporting HCP signature/name and date prior to submitting the form
Person preparing the report Name, Signature and Date	Please enter the information for the Syneos/CRP associate who prepared the report. If a Syneos associate, enter “Syneos” in the title field.

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Post Marketing Surveillance Pregnancy Report Form

Fax/Email to Syneos Health: fax: ***+1 800-800-1052***

email: ***palynziqpregnancystudy@syneoshealth.com***

Patient Information		
Patient ID	Date of Birth	Participating in 165-501? ☐ Yes ☐ No Subject ID#

Reporter Information		
Name of Reporter		HCP: ☐ Yes ☐No
HCP Type: ☐MD, ☐DO, ☐RN, ☐NP, ☐DDS	Specialty	
Country	email	phone

Palynziq Information			
Product: Palynziq	Dose: /mg	Frequency:	Route: SQ
Date of first Dose:		Stop Date of Palynziq:	
Date of most recent dose prior to LMP:		Lot#	Exp. Date:

Pregnancy Information		
Current Pregnancy		
Report of current pregnancy is:	☐ Prospective (currently pregnant, fetal outcome unknown)	☐ Retrospective (fetal outcome known)
Date of 1st day of LMP:	Estimated Due Date:	
Pregnancy Ongoing: ☐ Yes ☐ No	Pregnancy Type: ☐ Single ☐ Multiple # of fetus_____	
Obstetrical History (exclude current pregnancy)		
Any previous pregnancies:	Number with Palyzniq Exposure	Number without Palynziq Exposure
Total number previous pregnancies		
Number of full-term live births		
Number of pre-term live births		
Number of Spontaneous Abortion/Miscarriage		
Number of Therapeutic Abortion		
Number of Ectopic Pregnancy		
Number of Molar Pregnancy		
Number of Still Birth Gestational age in weeks		
Infants with congenital anomalies:		
Please provide the infant gender and congenital anomalies observed.		

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Post Marketing Surveillance Pregnancy Report Form

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email: ***palynziqpregnancystudy@syneoshealth.com***

Family History of Congenital Anomalies		
Does the patient have:		**Details**
Maternal family history of congenital anomalies?	☐**Yes** ☐**No**	
Paternal family history of congenital anomalies?	☐**Yes** ☐**No**	

Concurrent/Medical History		
Condition/Diagnosis	**Start Date**	**Stop Date or Ongoing Check box if ongoing**
		☐
		☐
		☐
		☐
		☐
		☐
		☐

Concomitant Medications (taken within 30 days of LMP/ or during pregnancy)					
Medication Name	**Indication**	**Dose**	**Freq**	**Start Date**	**Stop Date/Ongoing Check box if ongoing**
					☐
					☐
					☐
					☐
					☐
					☐
					☐

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Post Marketing Surveillance Pregnancy Report Form

Fax/Email to Syneos Health: fax: ***+1 800-800-1052***

email: ***palynziqpregnancystudy@syneoshealth.com***

Other Substance Exposure				
	Number	**Frequency**	**Start Date**	**Stop Date / Ongoing Check box if ongoing**
Tobacco				☐
Nicotine				☐
Marijuana/CBD				☐
Alcohol				☐
Recreational Substances Name/Type				☐
Name/Type				☐
Name/Type				☐

To the best of my knowledge, all information entered on this Safety report form is correct.

Physician's Name:

_____ _____ ____/_____/_____

Printed Title/Degree Signature Date dd/MMM/yyyy

Report prepared by (if other than Physician):

_____ _____ ____/_____/_____

Printed Title/Degree Signature Date dd/MMM/yyyy

Please complete all fields entering UNK or N/A if necessary

Submit Completed Report to *+1 800-800-1052 or palynziqpregnancystudy@syneoshealth.com* within 1 business day of learning of event

INSTRUCTIONS ONLY – DO NOT COMPLETE

Pregnancy Outcome Report Form

COMPLETION INSTRUCTIONS

165-504

Complete form print, sign and Fax/Email the Pregnancy Outcome Report Form to Syneos Health @

+1 800-800-1052 or email to palynziqpregnancystudy@syneoshealth.com within 1 business day of learning of the event.

The Pregnancy Outcome report form will be used to report the outcome of the pregnancy. The initial report of pregnancy will be captured on the Pregnancy Report Form.

Reporting Pregnancy Outcome Information & Correcting Erroneous Information

When reporting outcome information on patient pregnancy participating in the 165-504 registry, use the study specific pregnancy outcome report form. Do not leave any section blank, if the information is not available, please note in the appropriate sections. If after sending the report, updates or corrections are required, draw a single line through the incorrect information on the original form, then write in the new information, date and initial this new entry. **Please indicate on the fax coversheet, this report contains new information.**

Signatures

If the reporting Physician is completing the form, the physician should sign each iteration of the Safety Event Report Form that is sent to Syneos. If the CRP or Syneos associate is filling out the form during contact with the HCP, Syneos will enter the HCP name and title and complete the secondary signature line and enter Syneos Health in the title field. Please note for follow up reports, the reporting physician may initial and date behind their original signature for each subsequent updated report. This same convention also applies to the CRP/Syneos associate signatures.

Please contact Syneos for any questions regarding adverse event collection or reporting at **+1 833-672-2203.**

Pregnancy Outcome Form Instructions by Section

BMN 165-504	
General Information	
Patient ID	Enter the full subject number
Date of Birth	Enter the subject's Date of Birth using a DD-MMM-YYYY format (ex, 01-May-2001) reporting in accordance with local privacy rules
Participating in 165-501?	Check the appropriate box
Reporter Information	
Name of Reporter	Enter name of reporter
HCP	Check the appropriate box
HCP Type	Check the appropriate box
Specialty	Enter practice specialty if appropriate
Country	Enter country
email	Enter email address
Phone	Enter telephone number
Pregnancy Outcome Information	
Live Birth	Check the appropriate box
Date of Delivery	Enter the delivery date
Delivery Type	Check the appropriate box
Outcome	Check all appropriate fields and provide the date of the outcome, and the gestational age in weeks
Pregnancy /Labor/Delivery Complications	
Were there any complications during pregnancy	Check the appropriate box
Were there any complications during labor or delivery	Check the appropriate box
Complication	Check yes or no for each listed complication. If yes, provide the trimester the complication began. If other is selected, list the complication and the trimester in which it began. Note: if the complication arose during labor or delivery, enter this in the column for trimester at onset.
Maternal Phe levels	Please provide the highest Phe level for each month of pregnancy and additional levels if relevant to reported complications.
Prenatal Testing	
Were any prenatal tests performed.	Check the appropriate box
Test Type	List the test name, date test performed, indicate the test results were within normal limits by checking yes or no. If no, please provide a summary for the results.

Neonate Characteristics If more than one neonate per pregnancy, complete this section for each neonate and attach to the report submitted	
Infant ID	Enter Infant Study ID – mothers ID number, plus 2-digit number for infant. Note if multiples pregnancy, 2-digit infant number should reflect birth order. Complete a separate form for each Infant, it is acceptable to just complete the neonate characteristics, anomalies section and signature sections for additional neonates and attach to the fully completed form for submission.
Date of Birth	Check appropriate box, if yes, enter the type(s) of congenital anomalies.
Infant Sex	Check the appropriate box
Gestational Weeks at Birth	
1 Minute APGAR score	
5 Minute APGAR score	
Weight	
Length	
Head Circumference	
Physical Exam	Check the appropriate box. If No, complete the section below to provide information on observed abnormalities, congenital anomalies.
Abnormalities/ Congenital Anomalies Observed	
Anomaly	If the listed anomaly is observed, Check the appropriate box to indicate when the anomaly was first observed and provide the weeks at gestation. Please provide the severity, grade or degree of each reported anomaly. Indicated if treatment was provided by checking the appropriate box. Please provide any information regarding attribution of the anomaly and or contributing factors. If other is selected, Please enter the anomaly observed in the Anomaly column and provide the requested information as outlined above.

Signature Section	
HCP Name, Date	Please include the reporting HCP signature/name and date prior to submitting the form
Person preparing the report Name, Signature and Date	Please enter the information for the Syneos/CRP associate who prepared the report. If a Syneos associate, enter “Syneos” in the title field.

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Post Marketing Surveillance Pregnancy Outcome Report Form

Fax/Email to Syneos Health: fax: ***+1 800-800-1052***

email: ***palynziqpregnancystudy@syneoshealth.com***

Patient Information		
Patient ID	Date of Birth	Participating in 165-501? ☐ Yes ☐ No Subject ID#

Reporter Information		
Name of Reporter		HCP: ☐ Yes ☐No
HCP Type: ☐MD, ☐DO, ☐RN, ☐NP, ☐DDS	Specialty	
Country	email	phone

Pregnancy Outcome			
Live Birth ☐ Yes ☐ No	Date of Delivery		
Delivery Type:	☐Vaginal ☐Planned C-section ☐Unplanned C-section		
Outcome	**Check if Applicable**	**Date of Outcome**	**Gestational Age at Outcome (in weeks)**
Still Birth	☐		
Spontaneous Abortion	☐		
Therapeutic Abortion	☐		
Ectopic Pregnancy	☐		
Molar Pregnancy	☐		

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Post Marketing Surveillance Pregnancy Outcome Report Form

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email: ***palynziqpregnancystudy@syneoshealth.com***

Pregnancy /Labor /Delivery Complications		
Were there any complications during the pregnancy?	☐Yes ☐No	
Were there any complications during the labor or delivery?	☐Yes ☐No	
Complication	**Yes/No**	**Trimester at onset (**1st 2nd 3rd)
Hyperemesis Gravidarum	☐Yes ☐No	
Gestational Diabetes	☐Yes ☐No	
Gestational Hypertension	☐Yes ☐No	
Pre-eclampsia	☐Yes ☐No	
Eclampsia	☐Yes ☐No	
Pre-term labor not resulting in birth	☐Yes ☐No	
Placental Abruption	☐Yes ☐No	
Other: If yes, please provide details for each	☐Yes ☐No	

Maternal Phe Levels		
Phe level	Date	Trimester

Maternal Phe Levels		
Phe level	Date	Trimester

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Post Marketing Surveillance Pregnancy Outcome Report Form

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email: ***palynziqpregnancystudy@syneoshealth.com***

Prenatal Testing			
Were any prenatal tests performed?		☐Yes ☐No	
Test Name/Type	**Date Performed**	**Within Normal Limits**	**Abnormal Findings**
		☐Yes ☐No	
		☐Yes ☐No	
		☐Yes ☐No	
		☐Yes ☐No	
		☐Yes ☐No	
		☐Yes ☐No	
		☐Yes ☐No	
		☐Yes ☐No	
		☐Yes ☐No	
		☐Yes ☐No	

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Post Marketing Surveillance Pregnancy Outcome Report Form

Fax/Email to Syneos Health: fax: ***+1 800-800-1052***

email: ***palynziqpregnancystudy@syneoshealth.com***

Neonate Characteristics (Complete this section for each neonate)		
Infant ID	Date of Birth	Infant Sex: □F □ M □Unknown
Gestation Weeks at birth:	1 minute Apgar:	5-minute Apgar:
Weight:	Length:	Head circumference:
Physical Exam: Within Normal Limits: ☐Yes ☐No: If no, complete sections below		

Abnormalities/ Congenital Anomalies Observed				
Anomaly	**First Observed**	**Severity/Grade**	**Treatment**	**Attribution/ Contributing Factors**
Cleft Palate	☐In utero ☐Birth Age in weeks:		☐Yes ☐No	
Heart Defect	☐In utero ☐Birth Age in weeks:		☐Yes ☐No	
Microcephaly	☐In utero ☐Birth Age in weeks:		☐Yes ☐No	
Small Gestational Age	☐In utero ☐Birth Age in weeks:		☐Yes ☐No	
Other	☐In utero ☐Birth Age in weeks:		☐Yes ☐No	
Other	☐In utero ☐Birth Age in weeks:		☐Yes ☐No	
Other	☐In utero ☐Birth Age in weeks:		☐Yes ☐No	

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Post Marketing Surveillance Pregnancy Outcome Report Form

Fax/Email to Syneos Health: fax: ***+1 800-800-1052***

email: ***palynziqpregnancystudy@syneoshealth.com***

To the best of my knowledge, all information entered on this Safety report form is correct.
Physician's Name: _____ _____ _____ ___/_____/_____ Printed Title/Degree Signature Date dd/MMM/yyyy
Report prepared by (if other than Physician): _____ _____ ___/_____/_____ Printed Title/Degree Signature Date dd/MMM/yyyy
Please complete all fields entering UNK or N/A if necessary
Submit Completed Report to *+1 800-800-1052* or *palynziqpregnancystudy@syneoshealth.com* within 1 business day of learning of event

INSTRUCTIONS ONLY – DO NOT COMPLETE

Safety Event Report Form

COMPLETION INSTRUCTIONS

165-504

Complete form in PDF format, print, sign and Fax/Email the Safety Event Report Form to Syneos Health @

+1 800-800-1052 or email to palynziqpregnancystudy@syneoshealth.com within 24 hours of learning of the event.

Reporting Initial Information & Correcting Erroneous Information

The first Safety Event Report Form that is completed and faxed/emailed into Syneos Health for a given event is considered the 'Initial Report'. If information is unknown or not available at the time the Initial Report is prepared, the appropriate field should be marked as UNK or N/A. ***Please do not leave any fields blank.***

All Initial and Updated information should be recorded on the same Safety Event Report Form.

For updates and/or corrections, draw a single line through the incorrect information on the original printed Safety Event Report Form, write in the new information, and initial and date entry. **Please indicate clearly on the Fax Cover Sheet if the report is an updated report.**

Please summarize any additional relevant reports (e.g., discharge summary, autopsy reports, laboratory reports, pathology reports or other consultative reports). Please do not send copies of these reports with the report form unless requested by Syneos /BioMarin Pharmacovigilance (BPV). Black out the subject name and other subject identifiers (e.g., address, phone number, spouse name, parent name, etc.) prior to faxing or emailing these documents to Syneos Health. Only provide the subject's ID number.

Reporting Follow-Up Information

As soon as missing information or additional information becomes available, it should be reported on the original Safety Event Report Form. Remember to date and initial new information. This form and a fax coversheet should be completed, printed, signed and faxed/emailed to Syneos immediately.

Signatures

If the reporting healthcare professional (MD, DO, NP, RN, PA, DDS) is completing the form, the physician or HCP should sign each iteration of the Safety Event Report Form that is sent to Syneos. If the CRP or Syneos associate is filling out the form based on information received from the treating HCP, the CRP/Syneos will enter the HCP name and title and complete the secondary signature line. Please note for follow up reports, the reporting physician may initial and date behind their original signature for

each subsequent updated report. This same convention also applies to the CRP/Syneos associate signatures.

Please contact Syneos for any questions regarding adverse event collection or reporting at **+1 833-672-2203.**

Safety Event Report Form Instructions by Section

BMN 165-504	
General Information	
Subject Number	Enter the full subject number
Site Number	Enter the 4-digit site number
Subject Weight	Enter the subject's weight at the time of the event and indicate if the entry is in lbs. or kg.
Sex	Check the appropriate box to indicate sex.
Date of Birth	Enter the subject's Date of Birth using a DD-MMM-YYYY format (ex, 01-May-2001) reporting in accordance with local privacy rules
Investigational Product Information	
Product	This field will be pre-populated
Dose	Please provide the dose that the subject received at the time of the event
Frequency	Please provide the frequency of dose
Route	If patient is the mother, select SQ. If the patient is the offspring, select maternal exposure.
Date of first dose	Please provide the date of the mother's first dose
Date of the last dose	Enter the date of mother's most recent dose prior to event onset
Lot#/Expiration Date	This information can be located on the label on the drug kit.
Safety Event Information	
Safety Event Term	Please identify only one event term. Other related symptoms can be captured in the Description of Events section. If more than one safety event occurred (e.g. subject was hospitalized for surgery then developed a serious pneumonia), please complete separate Safety Event Report forms for each *reportable safety* event. **Please provide a medical diagnosis whenever possible.**
Event Onset Date/Time	Indicate the date/time the adverse event started.
Seriousness Criteria	Check all the boxes that apply. You *may* check more than one box but need only check one. For guidance: ***N/A:*** *Check this box if the HCP has assessed as non-serious.* ***Death****:* Any event resulting in fatal outcome. **L*ife-threatening****:* refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ***Hospitalization:*** refers to an event resulting in hospitalization as a direct cause of the event or prolongation of a hospitalization due to the event. An emergency room visit does not necessarily qualify as a hospitalization. ***Disability or incapacity***: refers to an event which results in a substantial disruption of a person's ability to conduct normal life functions. ***Important medical event***: refers to an event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed.

	Congenital Anomaly: refers to an event which is classified as a congenital anomaly in the offspring of the patient receiving the medication.
Severity	Grade refers to the severity of the Adverse Event. Please refer to the CTCAE for your protocol for a more detailed description of each severity grade. **Grade 1:** Mild/asymptomatic or mild symptoms/ clinical or diagnostic observations only/ intervention not indicated. **Grade 2:** Moderate / minimal, local or noninvasive intervention indicated / limiting age-appropriate instrumental activities of daily living e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc **Grade 3:** Severe or medically significant but not immediately life-threatening / hospitalization or prolongation of hospitalization indicated / disabling / limiting self-care with activities of daily living e.g, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden. **Grade 4:** Life-threatening or debilitating consequences/urgent intervention indicated **Grade 5:** Death related to AE.
Event Outcome	Indicate the outcome of the adverse event. If outcome is unknown due to subject being lost to follow up, please indicate.
Event related to Palynziq	Check the appropriate box
Is this event Device Related	Check the appropriate box
Infant Events Only Trimester of first infant exposure Was event breastfeeding at the time of the event	Check the appropriate box. Check the appropriate box.
Action taken with Study Drug as a result of event:	Check the appropriate box.
Description of Events	Provide a brief summary of the experience, including sequence of symptoms leading to adverse event, duration of event, specialty consultation, treatment medications, interventions, surgeries, or procedures that were a result of the event. Describe the final disposition of the subject's condition. For discharge summaries, autopsy reports, etc… please summarize the results. Do not attach results unless requested.
Relevant Reporting Information	
Subject Number	Please ensure this information is entered correctly
Relevant Concomitant/Pre-medications	List medications that the subject was taking at the time the adverse event occurred, including any pre-medication the subject received prior to the biospecimen collection procedure (if applicable). Please do not include treatment medication.
Suspect Medications other than Palynziq	List any medication suspected by the investigator as having caused or contributed to the event. Provide indication, dosing information, and dates for all suspect medications.
Other possible causes for event	Identify any other possible causes that may have caused or contributed to the event (e.g., underlying disease, new medical conditions, etc.)
Relevant Lab Results	List the results for any relevant laboratory tests performed in conjunction with the event. Please summarize all labs. Do not attach lab reports unless requested.

Relevant Medical History/Concomitant Diseases	List all other medically relevant conditions/pre-existing medical conditions the subject had at the time of the onset of the event. Relevant family history or other outstanding risk factors (smoking, alcohol, etc.)
HCP Name, Date	Please include the reporting HCP signature/name and date. With follow-up updates and/or corrections, please sign and date again.
Person preparing the report Name, Signature and Date	Please enter the information for the Syneos/CRP associate who prepared the report. If a Syneos associate, enter "Syneos" in the title field

165-504
Device Event Report Form Instructions (US Only)

Site #	Please enter the Site number
Subject #	Please enter the Subject's number
Safety Event Term Associated with this Event	Please enter the Safety Event Term associated with this Event
Event onset date	Please enter the Safety Event onset date using dd/MMM/yyyy format
Device Components	Please check yes or no. If yes, please enter date using dd/MMM/yyyy format
Kit #	Please enter the kit number. Do not leave field blank
UDI #	Please enter the UDI number
Lot #	Please enter the lot number listed on the PFS package
Expiration date	Please enter the expiration date
Operator	Please check the box indicating the operator of the device
Location of Event	Please check the box indicating the location where the event occurred
Date of Use	Please enter the date the device was opened/used
Device Returned	Please check yes or no
Date Returned	If yes, please enter the date using dd/MMM/yyyy format
HCP Name, Date	Please include the reporting HCP signature/name and date prior to submitting the form
Person preparing the report Name, Signature and Date	Please enter the information for the Syneos associate who prepared the report. If a Syneos associate, enter "Syneos" in the title field.

BMN 165-504

Post Marketing Surveillance Safety Event Report Form

Fax/Email to Syneos Health: fax: ***+1 800-800-1052***

email: ***palynziqpregnancystudy@syneoshealth.com***

Fax Please treat as confidential

To:	Syneos Health
Fax/email:	+1 800-800-1052 / ***palynziqpregnancystudy@syneoshealth.com***
Re:	Safety Event Source Documents, etc.
Pages:	_____, including this coversheet
Date faxed/emailed to BioMarin:	

Country of Origin	
Report Type	☐ Initial: _____ ☐ Follow-up: _____
From Site Contact:	***Sent by**: _____ ☐ MD ☐ RN ☐ Other: _____ Email: _____ Phone: _____

Comments:

BMN 165-504

Post Marketing Surveillance Safety Event Report Form

Fax/Email to Syneos Health: fax: ***+1 800-800-1052***

email: ***palynziqpregnancystudy@syneoshealth.com***

General Information

Subject Number:	Site Number:	Subject Weight: ☐ kg ☐ lbs	Sex: ☐ Male ☐ Female	Date of Birth: ___/_____/_____ dd/MMM/yyyy

BioMarin Product Information

Product: Palynziq	Dose: /mg	Frequency:	Route: SQ or Maternal Exposure

Date of first Maternal dose: ___/_____/_____ dd/MMM/yyyy

Date of last Maternal dose prior to event onset: ___/_____/_____ dd/MMM/yyyy

Expiration Date: ___/_____/_____ dd/MMM/yyyy

Lot Number(s): _____

Safety Event Information

Safety Event Term (report one diagnosis term only):

Event Onset date: ___/_____/_____ dd/MMM/yyyy

Onset time (24 hr clock i.e, 1:30 pm =13:30) _____

Seriousness Criteria: ☐N/A

☐ Death ☐ Life Threatening

☐ Hospitalization ☐ Disability

☐ *Important medical event ☐ Congenital anomaly

(*event jeopardized the patient or required intervention to prevent one of the events above)

Severity:

☐ Grade 1 (Mild) ☐ Grade 4 (Life Threatening)

☐ Grade 2 (Moderate) ☐ Grade 5 (Death)

☐ Grade 3 (Severe)

Event Outcome:

☐ Recovered/Resolved on ___/_____/_____ dd/MMM/yyyy

☐ Recovered/Resolved with sequelae on ___/_____/_____ dd/MMM/yyyy

☐ Not recovered/ Not resolved

☐ Recovering/Resolving

☐ Fatal (provide date of death) ___/_____/_____ dd/MMM/yyyy

Autopsy done: ☐ Yes ☐ No ☐ Unknown

☐ Lost to follow-up/Outcome unknown

Event related to Palynziq: ☐ Yes ☐ No

Is this event Device related?: ☐ Yes ☐ No

If yes, please complete the Device Reporting Form

Infant events only:

Trimester of First Infant Exposure - 1st 2nd 3rd

Was infant breastfeeding at the time of the event? ☐ Yes ☐ No

Action taken with Palynziq as a result of Event:

☐ Dose Not Changed ☐ Dose interrupted

☐ Drug Withdrawn ☐ Dose Reduced to _____/mg

☐ Unknown

☐ Not applicable (i.e.: event occurred within 30 days of final dose)

Description of Event(s): (Include dates, clinical course of events with treatments) - ENTER TREATMENT MEDICATIONS HERE

Subject Number:	Site Number:

Relevant Supporting Information

Relevant Concomitant Medications and Pre-Medications – DO NOT ENTER TREATMENT MEDICATIONS IN THIS FIELD

Suspect Medications: Are there any other medications suspected of causing or contributing to the event:

☐ Yes ☐ No (If Yes, List suspect product below)

Name and Indication:	Dose/Frequency/Route/Therapy dates(start/stop)

Were any other possible causes of the Event Identified: ☐Yes ☐ No If Yes, explain:

Relevant Laboratory Results (include dates and times if applicable):

Relevant Medical History (including history of similar event, concurrent illnesses, relevant surgeries, family or social history, etc.):

BMN 165-504

Post Marketing Surveillance Safety Event Report Form

Fax/Email to Syneos Health: fax: ***+1 800-800-1052***

email: ***palynziqpregnancystudy@syneoshealth.com***

To the best of my knowledge, all information entered on this Safety report form is correct.
Physician's Name: _____ _____ _____ ____/_____/_____ Printed Title/Degree Signature Date dd/MMM/yyyy
Report prepared by (if other than Physician): _____ _____ _____ ____/_____/_____ Printed Title/Degree Signature Date dd/MMM/yyyy
Please complete all fields entering UNK or N/A if necessary
Fax Complete Safety Event Term Report to Syneos Health 800-800-1052 or email palynziqpregnanctstudy@syneoshealth.com within 1 business day of learning of event

165-504
General Information
Subject Number: _____ **Site Number:** _____
Safety Event Term Associated with this Event: _____ *If more than 1 device component involved, complete a separate **Device Event Reporting** Form for each device.* SAE onset date: _____
Pre-Filled Syringe
Manufacturer Name: Cook Address: 1300 South Patterson Drive Bloomington, IN 47403 ☐ Needle ☐ Needle Cap ☐ Glass Syringe Barrel ☐ Plunger ☐ Passive Anti-Needle Stick Safety Guard **Kit #**:_____ **UDI #:** _____ **Lot #:** _____ **Expiration Date**: _____
Operator: ☐ HCP ☐ Patient ☐ Caregiver ☐ Other_____ **Location of Event:** ☐ Clinic ☐ Home ☐ Other_____ **Date of Use:** ___/_____/_____ ☐ N/A dd/MMM/yyyy **Device available for return?** ☐ Yes ☐ No **Device Returned:** ☐ Yes ☐ No

Physician's Name:

_____ _____ _____ ___/_____/_____
Printed Title/Degree Signature Date

Report prepared by (if other than Physician):

_____ _____ _____ ___/_____/_____
Printed Title/Degree Signature Date