Date of Genetically Modified HSC Infusion:

Time since autologous transplant and Genetically Modified HSC Infusion):

Day 0

3 month  6 months  1 /1.5 yr  2 /2.5 yr  3/3.5 yr  4/4.5yr  5yr

6yr  7yr  8 yr  9 yr  10 yr  11yr  12yr

13yr  14yr  15yr

Type of Hematopoietic Stem and Progenitor Cell (HSPC) Product: see DP CRF

**Hematological Status since the date of last report:**  Non-concerning  Concerning\*

The latest Complete Blood Count

Hb \_\_\_\_\_\_\_\_\_\_\_\_\_

WBC\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Plt\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Neutrophils %\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Lymphocytes%\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Retic Count\_\_\_\_\_\_\_\_\_\_\_\_\_

\***If concerning and clinically significant, complete AE form**

**Consider adding the following:**

**1) Was bone marrow aspirate/biopsy done prior to infusion?**

**Yes/no, date**

**If yes, then answer questions below**

**Is there evidence of Premalignant/Malignant Hematopoiesis?**

Dysplastic Cells  Yes  No

If Yes, Lineages affected\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Blasts.  Yes  No

If Yes, type\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Percentage\_\_\_\_\_\_\_\_\_\_

Is there marrow hypoplasia?  Yes  No

If Yes, indicate: myeloid lineage \_\_\_\_\_\_\_megakaryotic\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

What was M:E ratio: \_\_\_\_\_\_\_\_\_\_\_\_

**Additional questions to this section on bone marrow aspirate/biopsy**

1) Was cytogenetics tested?  Yes  No (FISH or karyotype)

Abnormalities  Yes  No

If yes, mark all that apply monosomy -5, -7, -13, -20 -Y, trisomy +8, +19, translocation t(1;3), t(2;11) t(3;3), t(3;21), t(6;9), t(11;16), deletion: del(3q)/3q-, del(5q)/5q-, del(7q) / 7q-, del (9q)/9q-, del 911q)/11q-, del (12p)/12p-, del 913q) / 13q-, del (20q)/20q-, inversion (3), other i17q and other abnormality (specify)

2) Was a genetic mutational panel performed?  Yes  No

If yes, attach copy of genetic mutational panel

**What best describes the abnormal hematopoiesis?**

MDS

Leukemia/lymphoma

Date of onset:

Is the event being treated?  Yes  No

Treatment:  Transfusions Blood Product\_\_\_\_\_\_\_\_\_\_\_\_\_ frequency\_\_\_\_\_\_\_

Chemotherapy

HSC Transplant

Has analysis been performed to determine probably cause of hematological toxicity?  Yes  No

**Is it related or likely due to the genetic manipulation**   Yes  No

If yes, specify relationship:

definitely related  probably related  possibly related  unrelated

**Is it related to the conditioning regimen**  Yes  No

If yes, specify relationship:

definitely related  probably related  possibly related  unrelated

**Bone Marrow Aspirate Performed?**  Yes  No

Normal Morphology  Dysplastic Morphology  Malignant morphology

Normal Cytogenetics  Abnormal Cytogenetics

Cytogenetic Abnormalities\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_(describe)

**Has the abnormal hematopoiesis resolved?** Yes  No

Date of resolution\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Survival Status

Alive

Dead Date Expired:

**SECTION A: FOR INTEGRATING VIRAL VECTOR PRODUCTS**

**Complete this Portion if Trial Involves Genetic Manipulation of HSPC using Integrating Viral Vectors (e.g. Lentiviruses)**

**Vector Specifics:** Transgene in the vector\_\_\_\_\_\_\_\_\_\_\_\_

Promoter/Enhancers in Vector \_\_\_\_\_\_\_\_\_\_

**Vector Copy Number (VCN) performed in**

Blood VCN\_\_\_\_\_\_\_\_ **CD3 depleted?** Yes  No

VCN in Specific Lineages: CD3+\_\_\_\_\_\_\_ CD19+\_\_\_\_\_\_ CD15+\_\_\_\_\_\_\_GPA+\_\_\_\_\_\_\_\_ CD14+\_\_\_\_\_\_

Percentage of Blood Cells Positive for Integrating Vector: PBMC \_\_\_\_\_\_\_\_\_ BFU-E\_\_\_\_\_\_\_\_\_\_

Bone Marrow VCN: BMMC\_\_\_\_\_\_ CD34+\_\_\_\_\_\_\_\_ CFC\_\_\_\_\_\_

Percentage of Bone Marrow Cells Positive for Integrating Vector: BMMC\_\_\_\_\_\_ CD34+\_\_\_\_\_\_\_\_ CFC\_\_\_\_\_\_

**Vector Integration Site Analysis (VISA) performed in**

Blood

Bone Marrow

Sorted/fractionated Cell Populations

(specify lineages) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Is there evidence of Polyclonal (“Rich”) Gene-Modified Hematopoiesis?**

Is there a “Rich” (polyclonal population with ≥1000 unique integrations) of minimally fractionated cell specimens (whole Bone Marrow, CD34+ cell product, whole blood)

Yes  No

Time Point\* Specimen Type Number of unique integrands Rich (Y/N) VCN

\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_` \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Yes  No \_\_\_\_

\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_` \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Yes  No \_\_\_\_

\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_` \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Yes  No \_\_\_\_

\*Time since infusion (0/0.5/1/1.5/2/2.5/3/3.5/4/4.5/5/6/7/8/9/10/11/12/13/14/15 yrs)

**Is there evidence of oligoclonal gene modified hematopoiesis?**

Yes  No

**Is there evidence of Clonal Dominance? i.e., Do any cell clone/s or integrant/s account for ≥20% of all clones?**

Yes  No

If Yes, List the site of integration of dominant (≥20% representation) clone/s [e.g. gene location or flanking gene location]

Gene Location Percent Representation/Relative Abundance

\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Is the location of the dominant integrant/s

Within or < 50Kb of a known oncogene

Within or <50Kb of a Transcriptional Unit of any gene

Within or < 50Kb of Cell signaling/proliferation Gene

Within or near the following genes known to be associated with insertional oncogenesis

LMO2

IKZF1

CCND2

HMGA2

MECOM

**Is there evidence of clonal expansion/Are any cell clones increasing in proportion over the last two analyses?**

Clone Last % representation/abundance Current % Abundance

\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Based on VCN and VISA, what best describes the gene-modified hematopoiesis?**

Clonal Dominance  Oligoclonal hematopoiesis  MDS

Leukemia/lymphoma

**SECTION B: FOR GENE EDITED CELLULAR PRODUCTS**

Complete this portion if Gene Edited HSPC product

Gene editing frequency performed:

Blood:

**CD3 depleted?**  Yes  No

Percent Conversion \_\_\_\_\_\_\_\_ or On-target Indels\_\_\_\_\_

Percent conversion in Specific Blood Lineages: CD3+\_\_\_\_\_\_\_ CD19+\_\_\_\_\_\_ CD15+\_\_\_\_\_\_\_GPA+\_\_\_\_\_\_\_\_ CD14+\_\_\_\_\_\_

On-target Indels in Specific Blood Lineages: CD3+\_\_\_\_\_\_\_ CD19+\_\_\_\_\_\_ CD15+\_\_\_\_\_\_\_GPA+\_\_\_\_\_\_\_\_ CD14+\_\_\_\_\_\_

Bone Marrow:

BMMC Percent Conversion \_\_\_\_\_\_\_\_ or On-target Indels\_\_\_\_\_

CD34+ Percent Conversion \_\_\_\_\_\_\_\_ or On-target Indels\_\_\_\_\_

CFC Percent Conversion \_\_\_\_\_\_\_\_ or On-target Indels\_\_\_\_\_

Off Target Interrogation: Bioinformatic:  CRISPOR  CRISTA

Other: list \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Number of off-target editing sites screened: \_\_\_\_\_\_\_\_\_

Number of off-target editing sites confirmed: \_\_\_\_\_\_\_\_

Checked by GUIDE-seq?  Yes  No

Confirmed by NGS?  Yes  No

Confirmed by other method: Yes No If yes, list: \_\_\_\_\_\_\_\_\_

Acceptable editing rate confirmed for each off-target editing site:

What is the location of the dominant off-target site(s):

Is the editing site location:  inter-genic  intra-genic

Translocations between on-target and off-target editing sites detected by:

Cytogenetics:  Yes  No

If yes, summarize: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Droplet Digital PCR:  Yes  No

If no, what is the limit of detection: \_\_\_\_\_\_\_\_\_\_\_\_

If yes, what is the frequency of detection: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

What method was used to monitor clonality:

On-target indels  Whole exome sequencing  Other\_\_\_\_\_\_\_\_

Do any cell clone/s associated with an editing event account for ≥20% of all clones?

Yes  No

If Yes, List the site of off-target gene editing of dominant (≥20% representation) clone/s [e.g. gene location or flanking gene location], if known

Gene Location Percent Representation/Relative Abundance

\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Is the location of the dominant gene editing site?  Yes  No

Within or < 50Kb of a known oncogene

Within or <50Kb of a Transcriptional Unit

Within or < 50Kb of Cell signaling/proliferation Gene

Are any cell clones increasing in proportion over the last two analyses?

Clone Last % representation Current % representation

If genotoxic event detected was an Oncogene panel used?   Yes  No

Was whole exome sequencing used?  Yes  No WGS?  Yes  No

If yes, state results: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

If genotoxicity developed, were pre-manipulated cells genetically analyzed for ChIP?  Yes  No

How: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

State results: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

FROM FDA DOCUMENT:

Since drug product infusion has there been.

New malignancy(ies)?

If yes, describe\_\_\_\_\_\_\_\_\_\_\_\_\_\_

New incidence or exacerbation of a pre-existing neurologic disorder?

Yes  No If yes, describe\_\_\_\_\_\_\_\_\_\_\_\_\_\_

New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder

Yes  No If yes, describe\_\_\_\_\_\_\_\_\_\_\_\_\_\_

New incidence of a hematologic disorder.

Yes  No If yes, describe\_\_\_\_\_\_\_\_\_\_\_\_\_\_

New incidence of infection (potentially product-related)

Yes  No If yes, describe\_\_\_\_\_\_\_\_\_\_\_\_\_\_