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