

BC2371 RDNA CONSTRUCT ON CHROMOSOME 3P1.1-2 IN R69 NEW ZEALAND WHITE RABBITS- bc2371 rdna construct on chromosome 3p1.1-2 in r69 new zealand white rabbits not applicable
LFB USA, Inc.

Bc2371 rDNA

Bc2371 rDNA CONSTRUCT IN R69 NEW ZEALAND WHITE RABBITS

LFB USA, Inc.

Bc2371 rDNA construct in R69 New Zealand white rabbits, expressing recombinant human Factor VII (rhFVII in the mammary gland).

Heritable construct

1. DESCRIPTION

A single copy of the rDNA construct (designated Bc2371) for human Factor VII (hFVII) has been integrated into the genome, on chromosome 3p1.1-2, of a specific, diploid line (designated R69) of hemizygous and homozygous New Zealand white rabbits (*Oryctolagus cuniculus*). This rDNA construct includes a chicken β -globin insulator sequence, the goat β -casein promoter at its 5' end, and the goat β -casein sequences at its 3' end. The integrated rDNA construct drives the expression of the rhFVII protein in the milk of R69 rabbits. The milk obtained from these rabbits is processed in order to purify and activate the rhFVII to rhFVIIa, which is then intended for use as a therapeutic for human hemophilia A or B patients with inhibitors to Factors VIII and IX.

2. WARNINGS AND PRECAUTIONS

R69 rabbits, or any materials derived from R69 rabbits, are not intended to enter the human or animal food supply.

3. EFFECTIVENESS

Multiple generations of the R69 line have demonstrated genetic stability as established through genetic tests for the presence of the Bc2371 rDNA construct, Bc2371 rDNA sequence fidelity, and Bc2371 construct integration site consistency. For each generation, phenotypic stability has been established based on the presence of recombinant hFVII zymogen in the milk of R69 line rabbits.

4. ANIMAL SAFETY

The health monitoring program for the rabbit population at the LFB USA's facility follows standardized operation procedures. The testing program characterizing the Specific Pathogen Free (SPF) status of the colony has been instituted based in part on the Federation of European Laboratory Animal Science Associations (FELASA) health monitoring recommendations, and in part on a European Note for Guidance on production and quality. The SPF health screening is performed as a health monitoring (modified sentinel testing) program and is performed on an established schedule (i.e. monthly at a minimum) to include animals that are statistically representative of the entire colony and population (sex, age). Established procedures govern action and any follow-up response to the CVM in the event of confirmed positive results for agents on the SPF exclusion list.

Quarterly morbidity and mortality summaries are prepared and evaluated based on daily health observations of LFB USA's rabbits colony. The morbidity (see Table 1 below) and mortality (see Table 2 below) provide a data summary for R69 lineage genetically engineered (GE) and wild type rabbits or non genetically engineered rabbit (non-GE) at the facility.

Table 1. Quarterly morbidity summary for Q1-Q4 2017 (Prevalence¹) in genetically engineered (GE) and non-GE rabbits.

	2017 Q1		2017 Q2		2017 Q3		2017 Q4	
	GE	Non-GE	GE	Non-GE	GE	Non-GE	GE	Non-GE
Rolling Population	680	106	654	100	687	100	753	111
Morbidity Cases (Integument) ²	113	6	81	2	90	6	117	5
Morbidity Cases (less Integument) ³	140	33	134	24	160	22	212	19
% Morbidity (less Integument) ⁴	20.6%	31.1%	20.5%	24.0%	23.3%	22.0%	28.2%	17.1%

¹Prevalence (% Morbidity) is the number new treatment/health cases in rabbits expressed as a percentage of rolling population for that quarter. Note that a rabbit may have more than one new case during a quarter.

²Total number of new morbidity cases attributed to hair/skin/integument only.

³Total number of new morbidity cases that include observations related to the following systems/categories: musculoskeletal, respiratory, reproductive, digestive, nervous, mammary, ophthalmic, urinary, behavior, and unthrifty/failure to thrive (integument excluded).

⁴% Morbidity (less integumentary) represents the number of new morbidity cases minus those cases attributed to hair/skin/integument expressed as a % of the rolling population for that quarter.

Table 2. Quarterly mortality summary for Q1-Q4 2017 (Prevalence¹) in genetically engineered (GE) and non-GE rabbits.

	2017 Q1		2017 Q2		2017 Q3		2017 Q4	
	GE	Non-GE	GE	Non-GE	GE	Non-GE	GE	Non-GE
Rolling Population	680	106	654	100	687	100	753	111
Mortality Cases ²	17	1	36	10	27	7	32	3
% Mortality	2.5%	0.9%	5.5%	10.0%	3.9%	7.0%	4.2%	2.7%

¹Prevalence (% Mortality) is the number of animals that died or were euthanized for cause in a period expressed as a percentage of rolling population for that quarter.

²Table captures mortalities due to spontaneous death and euthanasia for untreatable and serious health conditions (musculoskeletal, central nervous, ophthalmic, respiratory, urinary, and unthrifty/failure to thrive). Mortality in the table do not include euthanasia for purposes of routine colony population management purposes.

The rolling population, as captured in Tables 1 and 2 above, is the average of the monthly census for the facility for that quarter. The end of the month census is the total animal count the last day of the month but does not include kits who have not weaned. Therefore prevalence (% Morbidity) is the number of animals with new health cases in a period expressed as a percentage of the rolling population for a particular quarter. Table 2 for mortality does not include healthy rabbits submitted for SPF health screening purposes. Note that the facility population primarily consists of GE rabbits.

Even though the level of observation of GE production rabbits vs. non-GE rabbits was more rigorous, primarily due to the more intense nature of the reproductive and milking procedures (non-GE does were not machine milked) morbidity and mortality comparisons between GE and non-GE rabbits at the facility demonstrated a lack of adverse effect for the rDNA construct or its expression product.

5. LIMITATIONS OF USE

The R69 line of New Zealand white rabbits in the United States must be housed in only the LFB USA, Inc. facilities specified in the approved application.

Manufactured by:

LFB USA
 175 Crossing Boulevard
 Framingham, MA 01702

Approved by FDA under NADA 141-511

PRINCIPAL DISPLAY PANEL

NOT APPLICABLE

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Product Information				
Product Type	RECOMBINANT DEOXYRIBONUCLEIC ACID CONSTRUCT LABEL	Item Code (Source)	NDC:86047- 107	
Route of Administration	NOT APPLICABLE			
Active Ingredient/Active Moiety				
Ingredient Name	Basis of Strength	Strength		
BC2371 RDNA CONSTRUCT ON CHROMOSOME 3P1.1-2 IN R69 NEW ZEALAND WHITE RABBITS (UNE: 00PR6AZ75U) (BC2371 RDNA CONSTRUCT ON CHROMOSOME 3P1.1-2 IN R69 NEW ZEALAND WHITE RABBITS - UNE00PR6AZ75U)	BC2371 RDNA CONSTRUCT ON CHROMOSOME 3P1.1-2 IN R69 NEW ZEALAND WHITE RABBITS	1 [arbU] in 1 [arbU]		
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:86047-107-02	1 [arbU] in 1 NOT APPLICABLE; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
NADA	NADA141511	12/27/20 18		

Labeler - LFB USA, Inc. (079488639)

Revised: 11/2020

LFB USA, Inc.