EANM 2019 Abstract

A Novel Sn-117m Colloid for Human Radiosynoviorthesis Clinical Trials

N.R. Stevenson, C.A. Doerr, G.R. Gonzales, J. Simon, A. Bendele

Objectives:
In patients with advanced arthritis, direct injections of a radio-colloid into affected joints (radiosynoviorthesis a.k.a. radiosynovectomy) is used therapeutically to relieve pain and increase mobility. Isotopes such as Y-90, Re-186 and Er-169 are in routine clinical use. Recently, a Sn-117m (γ 159 keV, 86% ; e^- ~140 keV, 112% ; $t_{½}$ 14d) homogeneous colloid (HTC) has become available for treating canine osteoarthritis (OA). This product was modified with ascorbic acid (causing a color change) to differentiate it for human use. Studies were undertaken to demonstrate comparable physical and safety characteristics so that the product can be used in human trials.

Methods:
The addition of a small quantity of ascorbic acid to commercially available HTC results in a color change from yellow/orange to white. We anticipated that all other characteristics would remain unchanged as determined by measurements of particle size distributions, pH, endotoxicity, sterility, stability and free tin in solution performed in accordance with the established cGMP manufacturing procedures. Additionally, a study was undertaken to demonstrate that there were no *in-vivo* differences between the two products. Fourteen Sprague-Dawley rats (~ 120 g) were placed in 2 groups based on sex, totaling 7 male and 7 female rats in this study. All rats received HTC injected in the left knee, and the ascorbic acid homogeneous Sn-117m hydroxide colloid (AHTC) injection in the right knee. The planned dose administration was nominally 20 μCi (740 kBq) per injection for every rat, which scales in humans to about 12 mCi (444 MBq) or double the highest anticipated human knee dose. All rats were sacrificed at 42 days and both knees of each rat were harvested and fixed in formalin. The knees were sent for histopathological examination and a comparison of the left and right tissues.

Results:
There were no significant differences observed in the physical characteristics between the two colloidal preparations other than the desired color change. No significant histopathological differences were observed between the HTC and AHTC treated joints.

Conclusions:
An ascorbic Sn-117m homogeneous colloid has been developed specifically for human use. Other than the appearance (color) the physical and *in-vivo* characteristics are identical to the well-studied canine HTC product. The AHTC will now be used in upcoming human clinical trials in Canada.

04-24-19

Supporting Data

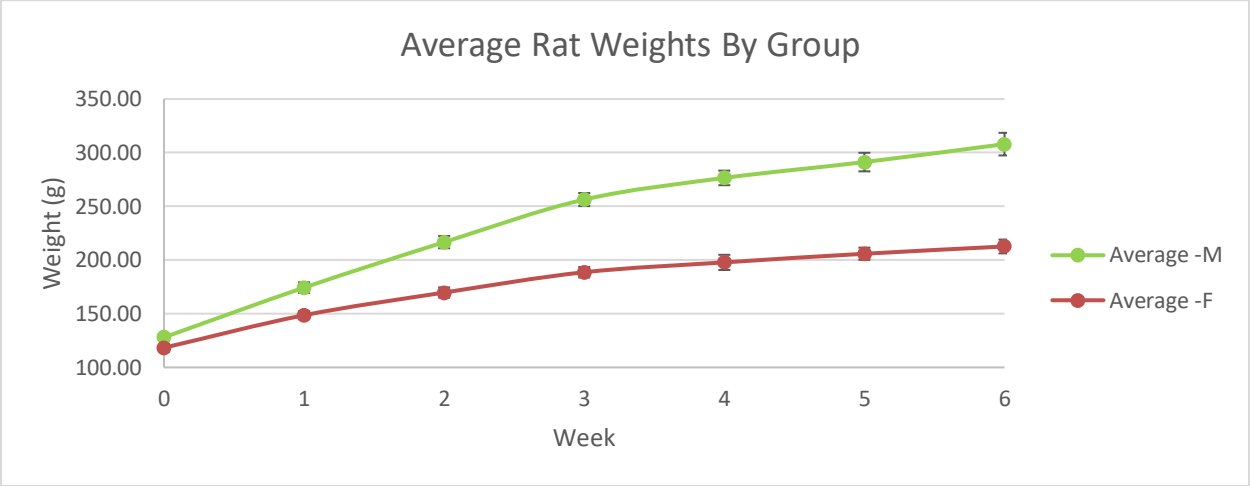

Table 2. Summary of Descriptive Histopathology Report

Group:		**Group 1**		**Group 2**	
Species:		**Rat (Sprague Dawley)**		**Rat (Sprague Dawley)**	
Sex:		**Male**		**Female**	
Necropsy Time Point:		**42 ± 2 Days Post-Dose**		**42 ± 2 Days Post-Dose**	
Animal No.:		**1-7**		**8-14**	
Treatment:		**Sn-117m colloid/Ascorbic Acid)**	**Sn-117m colloid**	**Sn-117m colloid/Ascorbic Acid)**	**Sn-117m colloid**
Joint:		**Right Knee**	**Left Knee**	**Right Knee**	**Left Knee**
# Evaluated:		7	7	7	7
Normal		2	4	3	2
Inflammation, synovium,	subacute, multifocal, very minimal	4	2	3	4
	subacute, multifocal, minimal			1	1
	subacute, multifocal or diffuse, mild	1	1		
Degeneration, articular cartilage,	focal, superficial, very minimal	3	2		
Degeneration, cruciate ligaments,	focal, mild		1		

Rat Study - SER-1

Dose Preparation

Prep #	Description:	Lot:		Date:
1	HTC	4125	Left Knee	11/28/2018
2	AHTC	4120	Right Knee	11/28/2018

						Right Knee Injection				Left Knee Injection								
Rat	Wt (g) at Admin.	Dosage	Dose Prep	Time (days)	Administration Date/Time	Activity Full (µCi)	Activity Empty (µCi)	Admin. Activity (µCi)	Inj. Qual.	Activity Full (µCi)	Activity Empty (µCi)	Admin. Activity (µCi)	Inj. Qual.	Scheduled Sacrifice Date/Time	Actual Sacrifice Date/Time	Elapsed Time (day)	Wt (g) at Sacrifice	Comments
M-1	123.2	low	1, 2	42	11/28/18 9:34 AM	25.1	2.6	**22.5**	1	24.9	7.8	**17.1**	1	1/9/19 9:34 AM	1/9/19 10:19 AM	42.0	300.0	none
M-2	129.5	low	1, 2	42	11/28/18 9:44 AM	28.9	25.8	**3.1**	1	29.8	3.6	**26.2**	1	1/9/19 9:44 AM	1/9/19 10:30 AM	42.0	292.0	none
M-3	132.4	low	1, 2	42	11/28/18 9:53 AM	25.4	1.3	**24.2**	1	26.0	3.2	**22.8**	1	1/9/19 9:53 AM	1/9/19 10:34 AM	42.0	324.6	none
M-4	133.8	low	1, 2	42	11/28/18 9:57 AM	30.3	3.2	**27.1**	1	23.7	3.2	**20.6**	1	1/9/19 9:57 AM	1/9/19 10:37 AM	42.0	300.6	none
M-5	122.3	low	1, 2	42	11/28/18 10:02 AM	28.1	1.9	**26.3**	1	30.2	2.5	**27.7**	2	1/9/19 10:02 AM	1/9/19 10:41 AM	42.0	314.2	L Blood seen after injection
M-6	129.5	low	1, 2	42	11/28/18 10:08 AM	26.7	2.6	**24.1**	1	25.2	3.0	**22.2**	1	1/9/19 10:08 AM	1/9/19 10:43 AM	42.0	328.0	none
M-7	125.8	low	1, 2	42	11/28/18 10:12 AM	24.0	2.6	**21.4**	1	27.7	2.6	**25.1**	2	1/9/19 10:12 AM	1/9/19 10:46 AM	42.0	296.7	L Blood seen after injection
F-8	124.0	low	1, 2	42	11/28/18 10:25 AM	23.9	1.7	**22.2**	1	31.7	2.9	**28.8**	1	1/9/19 10:25 AM	1/9/19 12:21 AM	41.6	202.3	none
F-9	116.0	low	1, 2	42	11/28/18 10:29 AM	24.6	2.6	**22.1**	1	25.7	0.9	**24.8**	1	1/9/19 10:29 AM	1/9/19 12:23 AM	41.6	220.4	none
F-10	110.3	low	1, 2	42	11/28/18 10:32 AM	28.5	3.6	**24.9**	1	23.8	1.7	**22.1**	1	1/9/19 10:32 AM	1/9/19 12:26 AM	41.6	213.7	none
F-11	121.9	low	1, 2	42	11/28/18 10:36 AM	27.0	2.3	**24.7**	1	29.9	1.7	**28.2**	1	1/9/19 10:36 AM	1/9/19 12:32 AM	41.6	226.2	none
F-12	122.6	low	1, 2	42	11/28/18 10:40 AM	30.4	3.3	**27.1**	1	30.0	2.4	**27.7**	1	1/9/19 10:40 AM	1/9/19 12:34 AM	41.6	214.5	none
F-13	114.3	low	1, 2	42	11/28/18 10:44 AM	25.2	2.4	**22.8**	1	30.9	1.9	**29.0**	2	1/9/19 10:44 AM	1/9/19 12:37 AM	41.6	204.2	L Blood seen after injection
F-14	119.3	low	1, 2	42	11/28/18 10:48 AM	28.5	2.9	**25.6**	2	24.6	2.8	**21.8**	1	1/9/19 10:48 AM	1/9/19 12:40 AM	41.6	207.6	R Blood seen after injection

Synovetin OA Test Methods and Specifications

Test*	Method[3]	Specification
Appearance	Visual	Cream, yellow or orange turbid particles[1]
pH	pH indicator paper or microprobe	6.5 - 9.0
Median Particle Size (PS)	Horiba Model LA-300 Particle Size Analyzer	2.5 – 6 µm
Particle Size Range (D10 to D90)	Horiba Model LA-300 Particle Size Analyzer	≥ 90% above 2.5 µm ≥ 90% below 20 µm
Endotoxin	Charles River Endosafe PTS	≤ 19 EU/mL
Sterility[2]	ISO 20857	SAL ≥ 10^{-4}
Activity concentration	Dose calibrator	2 – 4 mCi/mL (74 - 148 MBq/mL)
Specific activity	Gamma spectroscopy with ICP	0.25 – 0.5 mCi/mg (9.25 - 18.5 MBq/mg)
Shelf-life	--	2 weeks

*at activity reference time (end of manufacture)
[1]May settle on standing, but readily re-suspends with shaking.
[2]Retrospective test
[3]Appropriate method validation will be conducted for applicable methods