2.6.7 TOXICOLOGY TABULATED SUMMARY

TABLE OF CONTENTS

1 Toxicology: Overview

Test Article: KN035

Overview of Toxicological Studies of KN035

Type of Study/ Treatment Duration	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	GLP Compliance	Testing Facility	Report Number	Location in CTD
Single-Dose Toxicity								
	Sprague Dawley rat	intraperitoneal injection		10mg/kg	No	Alphamab	RDR-KN035-PD-2014-015	M4.2.2.2.3
	Cynomolgus Monkey	Intravenous injection (IV); subcutaneous injection (SC)		15 mg/kg (IV) 15, 30 mg/kg (SC)	No	JOINN & Alphamab	RDR-KN035-PD-2015-011	M4.2.2.2.1
Repeat-Dose Toxicity								
	Cynomolgus Monkey	Subcutaneous injection	4 weeks (QW, 5 doses)	5, 30, 150	Yes	NCSED	2015033-2*	M4.2.3.2.1
Local Tolerance								
No studies conducted. The injection sites were assessed in the 4-week repeat dose toxicity study conducted in monkeys.								
Other Studies								
In vitro								
TCR	Normal Cynomolgus monkey tissues	*in vitro*		5, 25μg/ml	Yes	WuXi App Tec	337-0003-IM	M4.2.3.7.7.1
TCR	Normal human tissues	*in vitro*	-	5, 25μg/ml	Yes	WuXi App Tec	337-0002-IM	M4.2.3.7.7.2
Hemolysis	Rabbit blood cells	*in vitro*	-	49.2mg/ml	Yes	NCSED	2015046	M4.2.3.7.7.3

Test Article: KN035

Overview of Toxicological Studies of KN035

Type of Study/ Treatment Duration	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	GLP Compliance	Testing Facility	Report Number	Location in CTD
In vivo								
Immunogenicity	Sprague Dawley rat	intraperitoneal injection	Single dose	10mg/kg	No	Alphamab	RDR-KN035-PD-2014-015	M4.2.2.2.3
	Cynomolgus Monkey	Intravenous injection; subcutaneous injection	Single dose	15, 30mg/kg (SC) 15mg/kg	No	Alphamab & JOINN	RDR-KN035-PD-2015-011	M4.2.2.2.1
	Cynomolgus Monkey	Intravenous injection; subcutaneous injection	Single dose	15mg/kg (IV) 5, 15,50mg/kg (SC)	No	NCSED	N2015042 Appendix 1	M4.2.2.2.2
	Cynomolgus Monkey	Subcutaneous injection	Repeat dose	5, 30, 150mg/kg (SC)	No	NCSED	2015033-2* Appendix V	M4.2.3.2.1
Immune toxicity	Cynomolgus Monkey	Subcutaneous injection	Repeat dose	5, 30, 150mg/kg (SC)	Yes	NCSED	2015033-2*	M4.2.3.2.1

*As there is no report number from NCSED, this number is assigned by 3D Medicines.

2 Toxicokinetics: Overview of Toxicokinetics Studies

Test Article: KN035

Type of Study/ Treatment Duration	Species and Strain	Method of Administration	Doses (mg/kg)	GLP Compliance	Testing Facility	Report Number	Location in CTD
Single- dose	Sprague Dawley rat	intraperitoneal injection (ip)	10mg/kg	No	Alphamab	RDR-KN035-PD-2014-015	M4.2.2.2.3
Single- dose	Cynomolgus Monkey	Intravenous injection; subcutaneous injection	15 mg/kg (IV) 15, 30 mg/kg (SC)	No	Alphamab & JOINN	RDR-KN035-PD-2015-011	M4.2.2.2.1
4-week Repeat	Cynomolgus Monkey	Subcutaneous injection	5, 30, 150mg/kg	Yes	NCSED	2015033-2*	M4.2.3.2.1

*As there is no report number from NCSED, this number is assigned by 3D Medicare.

3 Toxicokinetics: Overview of Toxicokinetics Data

Test Article: KN035

Lot. No. PC20140513

Species	Daily Dose (mg/kg)	Sample collection time points	AUC_{last} h*mg/mL	AUC_{INF} h*mg/mL	$AUC_{(0-168h)}$ h*mg/mL	Study Duration, Dosing	GLP Compliance	Study Number
SD rat (ip)	10	before dosing:0 min; after dosing: 15min, 1h, 2h, 8h, 1d, 2d, 4d, 7d, 11d, 15d, 21d, 28d.	2.79	3.04	2.39	Single dose	No	RDR-KN035-PD-2014-015

Test Article: KN035

Lot. No. 150107

Species	Daily Dose (mg/kg)	Sample collection time points	AUC_{last}	AUC_{INF_obs}	$AUC_{(0\text{-}240\ h)}$	$AUC_{(0\text{-}408\ h)}$	Study Duration, Dosing	GLP Compliance	Study Number
			h*mg/mL	h*mg/mL	h*mg/mL	h*mg/mL			
Cynomolgus Monkey	SC low-dose（15 mg/kg）	KN035 SC group: Predose (0 hr); after dose 1、 4, 8, 12hr; 1, 2, 3, 5, 7, 10, 14, 17, 24, 32days; KN035 IV group: Predose (0 hr); immediately after dose, 15min, 2, 8 hrs, 1, 3, 7, 10, 14, 17, 24, 32days.	15.37	15.38	11.62	14.22	Single dose	No	RDR-KN035-PD-2016-011
	SC high-dose（30 mg/kg）		25.78	25.83	21.00	24.60	Single dose		
	Intravenous（15 mg/kg）		17.18	17.20	15.35	NA	Single dose		

NA: No statistics

Test Article: KN035

Lot. No. 20150502FB

Species	Daily Dose (mg/kg)	Date		Sample collection time points	$AUC_{(0-t)}$ h*ng/mL	$AUC_{(0-\infty)}$ h*ng/mL	Study Duration, Dosing	GLP Compliance	Study Number
Monkey (SC)	5	1st dose	M: 5	pre-dose, after first dose 2h、6h、24h、48h、96h, pre-2nd dose, pre-3rd dose, pre-4th dose, pre-5th dose, after 5th dose 2h、6h、24h、48h、 96h and 7day、10day、14day and 28day	5628246	8200930	4 weeks (QW, 5 doses)	Yes	2015033-2*
			F: 5		3216974	6399645			
		5thdose	M: 5		9295921	1059664839			
			F: 5		5846570	7408957			
	30	1st dose	M: 5		27460655	38670699			
			F: 5		19517602	28766460			
		5thdose	M: 5		39910435	76651694			
			F: 5		38756709	70048693			
	150	1st dose	M: 5		48425354	71712755			
			F: 5		100367900	143107451			
		5thdose	M: 5		89375517	143372279			
			F: 5		168019414	271306454			

*As there is no report number from NCSED, this number is assigned by 3D Medicines.

4 Toxicology: Drug Substance

Test Article: KN035

Drug Substance-Characteristics of Batch used in GLP Toxicological Studies

Batch/Lot No.	Concentration	Purity	Report Number	Type of Study	Location in CTD
20150502FB#	196.78 mg/mL	99.5%	2015033-2*	4-week repeat dose toxicity in monkeys; Immunogenicity; Immune toxicity	M4.2.3.2.1
			N2015042	Immunogenicity	M4.2.2.2.2
			2015046	*In vitro* hemolysis test	M4.2.3.7.7.3
			337-0003-IM	Tissue cross-reactivity with Cynomolgus monkey tissues	M4.2.3.7.7.1
			337-0002-IM	Tissue cross-reactivity with human tissues	M4.2.3.7.7.2

#samples used for nonclinical studies are aliquoted from 20150502 prior to vialing of 20150502 DP, and renamed 20150502FB

*As there is no report number from NCSED, this number is assigned by 3D Medicare.

5 Single Dose Toxicity:

Test Article: KN035

Species and Strain	Method of Administration (Vehicle/Formulation)	Dose (mg/kg)	Gender and No. per-Group	Lethal dose (mg/kg)	Noteworthy Findings	Report Number
SD rat	intraperitoneal injection (ip)	10mg/kg	5/group/sex	None	there were no abnormal clinical phenomena noted during the experiment, such as appearance, activity, coat, urine, feces and so on.	RDR-KN035-PD-2014-015
Cynomolgus Monkey	Intravenous injection (IV); subcutaneous injection (SC)	15 mg/kg (IV) 15, 30 mg/kg (SC)	1/group/sex	None	There were no abnormal clinical signs observed in the animals during the study, such as unusual behavior and changes in food consumption.	RDR-KN035-PD-2016-011

6 Repeat Dose Toxicity

Test Article: KN035

Report title: Four-Week Repeated Dose Toxicity Study of KN035 by Subcutaneous Injection to Cynomolgus Monkeys with a Four-Week Recovery Period (Repeated Dose Toxicity)

Species/Strain:
Cynomolgus monkey

Initial Age: 3 to 4 years

Date of First Dose (Females/ Males):
Aug. 12/13, 2015

Duration of Dosing:
4 weeks (QW, 5 doses)

Duration of Post dose:

Method of Administration:
Subcutaneous injection

Vehicle/Formulation:
Test Article could be used directly without any more preparation

Report Number:2015033-2

Location in CTD:M4.2.3.2.1

GLP Compliance: Yes

Special Features: Immune toxicity assessment, anti-drug antibodies and ECG

No observed Adverse Effect Level :>150mg/kg

Daily Dose (mg/kg)	0 (Control)		5		30		150	
Number of Animals	**M:5**	**F: 5**	**M:5**	**F: 5**	**M:5**	**F: 5**	**M: 5**	**F: 5**
Toxicokinetics: C_{max} (μg/mL)								
1st dose	-	-	78462	32099	660908	212857	503380	1090458
5th dose	-	-	64589	50556	341478	322809	800900	1371876
Toxicokinetics: AUC $_{(0-t)}$ (ngxhr/mL)								
1st dose	-	-	5628246	3216974	27460655	19517602	48425354	100367900
5th dose	-	-	9295921	5846570	39910435	38756709	89375517	168019414
Toxicokinetics: AUC $_{(0-\infty)}$ (ngxhr/mL)								

Test Article: KN035

Report title: Four-Week Repeated Dose Toxicity Study of KN035 by Subcutaneous Injection to Cynomolgus Monkeys with a Four-Week Recovery Period (Repeated Dose Toxicity)

Species/Strain:
Cynomolgus monkey

Initial Age: 3 to 4 years

Date of First Dose (Females/ Males):
Aug. 12/13, 2015

Duration of Dosing:
4 weeks (QW, 5 doses)

Duration of Post dose:

Method of Administration:
Subcutaneous injection

Vehicle/Formulation:
Test Article could be used directly without any more preparation

Report Number:2015033-2

Location in CTD:M4.2.3.2.1

GLP Compliance: Yes

Special Features: Immune toxicity assessment, anti-drug antibodies and ECG

No observed Adverse Effect Level :>150mg/kg

Daily Dose (mg/kg)	**0 (Control)**		**5**		**30**		**150**	
Number of Animals	**M:5**	**F: 5**	**M:5**	**F: 5**	**M:5**	**F: 5**	**M: 5**	**F: 5**
1st dose	-	-	8200930	6399645	38670699	28766460	71712755	143107451
5th dose	-	-	1059664839	7408957	76651694	70048693	143372279	271306454
Noteworthy Finding[a]								
Died or Sacrificed Moribund	-	-	-	-	-	-	-	-
Clinical observation	-	-	-	-	-	-	-	-
Body weight & food consumption	-	-	-	-	-	-	-	-
Body temperature	-	-	-	-	-	-	-	-
ECG	-	-	-	-	-	-	-	-
Blood pressure	-	-	-	-	-	-	-	-
Hematological exanimation	-	-	-	-	-	-	-	-
Serum biochemistry	-	-	-	-	-	-	-	-
Urianalysis	-	-	-	-	-	-	-	-

Test Article: KN035

Report title: Four-Week Repeated Dose Toxicity Study of KN035 by Subcutaneous Injection to Cynomolgus Monkeys with a Four-Week Recovery Period (Repeated Dose Toxicity)

Species/Strain:
Cynomolgus monkey

Initial Age: 3 to 4 years

Date of First Dose (Females/ Males):
Aug. 12/13, 2015

Duration of Dosing:
4 weeks (QW, 5 doses)

Duration of Post dose:

Method of Administration:
Subcutaneous injection

Vehicle/Formulation:
Test Article could be used directly without any more preparation

Report Number:2015033-2

Location in CTD:M4.2.3.2.1

GLP Compliance: Yes

Special Features: Immune toxicity assessment, anti-drug antibodies and ECG

No observed Adverse Effect Level :>150mg/kg

Daily Dose (mg/kg)	0 (Control)		5		30		150	
Number of Animals	**M:5**	**F: 5**	**M:5**	**F: 5**	**M:5**	**F: 5**	**M: 5**	**F: 5**
Ophthalmoscopy	-	-	-	-	-	-	-	-
CD4+ CD8+Tlymphocyte	-	-	-	-	-	-	-	-
Serum hormone	-	-	-	-	-	-	-	-
Organ Weights	-	-	-	-	-	-	-	-
Pathology	-	-	-	-	-	-	-	-

-: No abnormal findings

[a]: numbers of animals with positive result was reported

Test Article: KN035

Report title: Four-Week Repeated Dose Toxicity Study of KN035 by Subcutaneous Injection to Cynomolgus Monkeys with a Four-Week Recovery Period (Repeated Dose Toxicity)

Species/Strain: Cynomolgus monkey

Duration of Dosing: 4 weeks (QW, 5 doses)

Report Number: 2015033-2

Sex			**Male**				**Female**			
Daily Dose (mg/kg)			**0 (Control)**	**5**	**30**	**150**	**0 (Control)**	**5**	**30**	**150**
Animal number			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
Tissue	**Abnormal**	**Degree**	**Observed animal number**							
Microscopic pathology (at the end of dosing phase)										
Liver										
	Infiltration, mononuclear cell	+	1	3	0	1	0	3	2	1
	Granuloma, with necrosis and mineralization	++	0	0	0	0	1	0	0	0
Heart										
	Infiltration, mononuclear cell	+	1	2	1	1	0	2	1	2
		++	0	0	0	1	0	0	0	1
Lungs(with bronchi)										
	Infiltration, mononuclear cell, pleura	+	0	0	1	0	0	0	2	1
	Hemorrhage, alveolar	+	0	0	0	0	0	1	1	0
		++	0	0	0	1	0	0	0	0
Kidney										
	Infiltration, mononuclear cell, cortex	+	3	1	1	2	2	1	2	2
		++	0	1	0	0	0	1	0	0
Spleen										
	Increased tingible body macrophages, follicles	+	0	1	1	1	0	0	0	2
		++	0	0	0	0	0	0	1	0
	Increased mitosis, follicles	++	0	0	0	0	1	0	0	0

Test Article: KN035

Report title: Four-Week Repeated Dose Toxicity Study of KN035 by Subcutaneous Injection to Cynomolgus Monkeys with a Four-Week Recovery Period (Repeated Dose Toxicity)

Species/Strain: Cynomolgus monkey

Duration of Dosing: 4 weeks (QW, 5 doses)

Report Number: 2015033-2

Sex			**Male**				**Female**			
Daily Dose (mg/kg)			**0 (Control)**	**5**	**30**	**150**	**0 (Control)**	**5**	**30**	**150**
Animal number			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
Tissue	**Abnormal**	**Degree**	**Observed animal number**							
Microscopic pathology (at the end of dosing phase)										
	Hyaline material, follicles	+	0	1	0	1	0	0	0	1
Thymus										
	Cyst(s)-Present	/	0	1	1	2	1	2	0	0
	Decreased lymphocytes, cortex	+	0	0	0	0	2	0	0	0
Submaxillarygland										
	Infiltration, mononuclear cell	+	1	3	3	2	1	1	2	2
Inguinal lymphnodes										
	Erythrocytosis/phagocytosis	+	2	1	1	0	1	0	0	0
		++	1	1	1	0	0	0	0	0
	Pigment	+	3	1	2	0	0	0	0	0
Mesentericlymph nodes										
	Macrophages, pigmented	+	1	0	0	0	0	0	0	0
Thyroid										
	Ectopic tissue, thymus	/	2	1	0	0	0	0	0	0
	Cyst(s)-Present	/	0	1	0	0	0	0	0	0
Mass next to thymus										
	Granuloma, with necrosis	++	1	0	0	0	0	0	0	0

Test Article: KN035

Report title: Four-Week Repeated Dose Toxicity Study of KN035 by Subcutaneous Injection to Cynomolgus Monkeys with a Four-Week Recovery Period (Repeated Dose Toxicity)

Species/Strain: Cynomolgus monkey

Duration of Dosing: 4 weeks (QW, 5 doses)

Report Number: 2015033-2

Sex			**Male**				**Female**			
Daily Dose (mg/kg)			**0 (Control)**	**5**	**30**	**150**	**0 (Control)**	**5**	**30**	**150**
Animal number			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
Tissue	**Abnormal**	**Degree**	**Observed animal number**							
Microscopic pathology (at the end of dosing phase)										
	and mineralization									
Mass next to lung										
	Granuloma, with necrosis and mineralization	+++	1	0	0	0	0	0	0	0
Pituitary										
	Cyst(s)-Present	/	0	0	0	0	0	0	1	1
	Glial nodules, pars nervosa	+	0	0	0	0	0	0	1	0
Ovary										
	Cyst(s)-Present	/	\	\	\	\	0	1	0	0
Skeletal muscle										
	Infiltration, mononuclear cell	+	0	1	0	0	0	0	0	0
		++	0	0	0	1	0	0	0	0
Testis										
	Immature - Present	/	2	2	3	3	\	\	\	\
Epidiymis										
	Immature - Present	/	2	2	3	3	\	\	\	\
Urinary bladder										
	Infiltration, mononuclear cell	++	0	0	0	0	0	0	0	1

Test Article: KN035

Report title: Four-Week Repeated Dose Toxicity Study of KN035 by Subcutaneous Injection to Cynomolgus Monkeys with a Four-Week Recovery Period (Repeated Dose Toxicity)

Species/Strain: Cynomolgus monkey

Duration of Dosing: 4 weeks (QW, 5 doses)

Report Number:2015033-2

Sex			**Male**				**Female**			
Daily Dose (mg/kg)			**0 (Control)**	**5**	**30**	**150**	**0 (Control)**	**5**	**30**	**150**
Animal number			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
Tissue	**Abnormal**	**Degree**	**Observed animal number**							
Microscopic pathology (at the end of dosing phase)										
Skin (rectum)										
	Infiltration, mononuclear cell, dermis/subcutis	++	0	0	0	0	0	0	1	0
	edema, muscularis	++	0	0	0	0	0	0	1	0
Skin(mammarygland)										
	Infiltration, mononuclear	+	0	0	0	0	0	0	0	1
	cell, dermis/subcutis	++	0	0	0	0	0	0	1	0

No micropathology changes were observed in cerebrum, parathyroid(2), spinal cord(cervical, thoracic, lumbar), sternum with bone marrow, aorta, tongue, trachea, esophagus, gall bladder, adrenal gland(2), pancreas, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, epididymis(2), prostate, seminal vesicle, uterus (with cervix), oviduct, urinary bladder, sciatic never, mammary gland (female only), femur, eye(2), optic never(2), lymph nodes(mesenteric).

Notes： “-” no micropathology change, “+” minimal change, “++” mild change, “+++” moderate change, “++++” marked change,. “/”Don’t grade, “/”There are no these tissues in male or female Parathroid missing: FD401. One side of parathyroid missing: MD402, MD403, FD102, FD403.

Test Article: KN035

Report title: Four-Week Repeated Dose Toxicity Study of KN035 by Subcutaneous Injection to Cynomolgus Monkeys with a Four-Week Recovery Period (Repeated Dose Toxicity)

Species/Strain: Cynomolgus monkey

Duration of Dosing: 4 weeks (QW, 5 doses)

Report Number:2015033-2

Sex			**Male**				**Female**			
Daily Dose (mg/kg)			**0 (Control)**	**5**	**30**	**150**	**0 (Control)**	**5**	**30**	**150**
Animal number			**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Tissue	**Abnormal**	**Degree**	**Observed animal number**							
Microscopic pathology (at the end of recovery phase)										
Heart										
	Infiltration, mononuclear cell	+	2	1	2	1	1	0	0	1
		++	0	0	0	1	0	0	0	0
	Degeneration, myocardial	+	1	0	0	1	0	0	0	0
Lung (with bronchi)										
	Hemorrhage, alveolar	+	0	1	2	0	0	0	0	0
	Infiltration, mononuclearcell, pleura	+	0	0	0	0	0	1	0	0
	Granuloma, with necrosis and mineralization	+	0	0	0	0	0	0	0	0
Mass of Lung										
	Granuloma, with necrosis and mineralization	++	0	0		0	0	0	1	0
Liver										
	Infiltration, mononuclear cell	+	1	2	1	1	1	1	0	0
	Infiltration, eosinophil	++	0	0	1	0	0	0	0	
Spleen										
	Increased	+	1	1	1	1	1	1	0	1
	tingiblebodymacrophages,	++	1	1	1	0	1	0	0	0

Test Article: KN035

Report title: Four-Week Repeated Dose Toxicity Study of KN035 by Subcutaneous Injection to Cynomolgus Monkeys with a Four-Week Recovery Period (Repeated Dose Toxicity)

Species/Strain: Cynomolgus monkey

Duration of Dosing: 4 weeks (QW, 5 doses)

Report Number: 2015033-2

Sex			**Male**				**Female**			
Daily Dose (mg/kg)			**0 (Control)**	**5**	**30**	**150**	**0 (Control)**	**5**	**30**	**150**
Animal number			**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Tissue	**Abnormal**	**Degree**	**Observed animal number**							
Microscopic pathology (at the end of recovery phase)										
	follicles									
	Decreased lymphocytes, white pulp	+	0	0	0	0	0	0	1	0
		++	0	0	0	0	0	1	0	0
	Pigment, follicles	+	0	0	0	0	0	0	0	0
	Hyaline material, follicles	+	1	0	0	0	0	0	0	0
Kidney										
	Infiltration, mononuclear cell, cortex	+	2	2	1	2	1	2	0	1
Submaxillarygland										
	Infiltration, mononuclear cell	+	1	2	1	1	1	0	1	1
Thymus										
	Cyst(s)-Present	/	0	2	1	1	0	0	0	0
	Decreased lymphocytes,cortex	+	0	0	0	0	0	0	2	1
Thyroid										
	Cyst(s)-Present	/	0	1	0	1	0	0	0	0
Pancreas										

Test Article: KN035

Report title: Four-Week Repeated Dose Toxicity Study of KN035 by Subcutaneous Injection to Cynomolgus Monkeys with a Four-Week Recovery Period (Repeated Dose Toxicity)

Species/Strain: Cynomolgus monkey

Duration of Dosing: 4 weeks (QW, 5 doses)

Report Number:2015033-2

Sex			**Male**				**Female**			
Daily Dose (mg/kg)			**0 (Control)**	**5**	**30**	**150**	**0 (Control)**	**5**	**30**	**150**
Animal number			**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Tissue	**Abnormal**	**Degree**	**Observed animal number**							
Microscopic pathology (at the end of recovery phase)										
	Vaculoation, glandular epithelial cell	++	0	1	0	0	0	0	0	0
Inguinal lymphnodes										
	Erythrocytosis/phagocytosis	+	0	0	1	0	0		0	0
	Histiocytosis	+	0	0	0	1	0	0	0	0
	Hemorrhage	+	0	0	0	0	0	0	0	1
Mesentericlymph nodes										
	Granuloma with calcification	+	1	0	0	0	0	0	0	0
Pituitary										
	Cyst(s)-Present	/	0	0	0	1	1	0	0	0
Skeletalmuscle										
	Infiltration, mononuclear cell	+	0	0	1	0	0	0	0	0
Ovary										
	Cyst(s)-Present	/	\	\	\	\	0	1	0	1
Skin										
	Infiltration, mononuclear cell, dermis/subcutis	+	0	0	1	0	0	0	0	0
Skin (rectum)										
	Infiltration, mononuclear cell, dermis/subcutis	++	0	0	0	0	1	0	0	0

Test Article: KN035

Report title: Four-Week Repeated Dose Toxicity Study of KN035 by Subcutaneous Injection to Cynomolgus Monkeys with a Four-Week Recovery Period (Repeated Dose Toxicity)

Species/Strain: Cynomolgus monkey

Duration of Dosing: 4 weeks (QW, 5 doses)

Report Number:2015033-2

Sex			**Male**				**Female**			
Daily Dose (mg/kg)			**0 (Control)**	**5**	**30**	**150**	**0 (Control)**	**5**	**30**	**150**
Animal number			**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Tissue	**Abnormal**	**Degree**	**Observed animal number**							
Microscopic pathology (at the end of recovery phase)										
Mass of Skin										
	Granuloma, with necrosis and mineralization	+++	0	0	0	1	0	0	0	0
Brain										
	Vascular anomaly	++	0	0	0	1	0	0	0	0
Trachea										
	Infiltration, mononuclear cell	+	1							
Tongue										
	Infiltration, mononuclear cell	+	1							
Testis										
	Immature - Present	/	2	2	2	2	\	\	\	\
Epididymis										
	Immature - Present	/	2	2	2	2	\	\	\	\

No micropathology changes were observed in cerebrum, parathyroid(2), spinal cord(cervical, thoracic, lumbar), thymus, sternum with bonemarrow, aorta, tongue, trachea, esophagus, gall bladder, adrenal gland(2), stomach, duodenum, jejunum, ileum, cecum, colon, rectum, testis(2),epididymis(2), seminal vesicle, uterus (with cervix), oviduct, urinary bladder, sciatic never, mammary gland (female only), femur, eye(2), opticnever(2).

Notes: "-" no micropathology change, "+" minimal change, "++" mild change, "+++" moderate change, "++++" marked change. "/"Don't grade, "/"There are no these tissues in male or female. Parathroid missing:MD304, MD405, FD405. Prostate missing: MD104. One side of parathyroid missing: MD105, MD404, FD404.

16 Local Tolerance

Test Article: KN035

Report title: Four-Week Repeated Dose Toxicity Study of KN035 by Subcutaneous Injection to Cynomolgus Monkeys with a Four-Week Recovery Period (Repeated Dose Toxicity)

Species/Strain: Cynomolgus monkey

Duration of Dosing: 4 weeks (QW, 5 doses)

Report Number: 2015033-2

Sex			**Male**				**Female**			
Daily Dose (mg/kg)			**0 (Control)**	**5**	**30**	**150**	**0 (Control)**	**5**	**30**	**150**
Animal number			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
Tissue	**Abnormal**	**Degree**	**Observed animal number**							
Microscopic pathology (at the end of dosing phase)										
Injection site										
	Infiltration, mononuclear	+	2	2	2	1	1	2	2	1
	cell, dermis/subcutis	++	0	1	1	1	2	0	1	1
	Infiltration, neutrophil,	+	0	0	0	1	0	0	0	0
	dermis/subcutis	++	0	0	1	0	2	0	0	0
	Infiltration, mixed cell,	+	0	0	0	0	0	1	0	0
	dermis/subcutis	++	0	0	0	0	0	0	0	1
	Erosion, epithelium	++	0	0	1	0	0	0	0	0

No micropathology changes were observed in cerebrum, parathyroid(2), spinal cord(cervical, thoracic, lumbar), thymus, sternum with bonemarrow, aorta, tongue, trachea, esophagus, gall bladder, adrenal gland(2), stomach, duodenum, jejunum, ileum, cecum, colon, rectum, testis(2),epididymis(2), seminal vesicle, uterus (with cervix), oviduct, urinary bladder, sciatic never, mammary gland (female only), femur, eye(2), opticnever(2).

Notes: "-" no micropathology change, "+" minimal change, "++" mild change, "+++" moderate change, "++++" marked change. Parathroid missing: MD304, MD405, FD405. Prostate missing: MD104. One side of parathyroid missing: MD105, MD404, FD404.

Test Article: KN035

Report title: Four-Week Repeated Dose Toxicity Study of KN035 by Subcutaneous Injection to Cynomolgus Monkeys with a Four-Week Recovery Period (Repeated Dose Toxicity)

Species/Strain: Cynomolgus monkeys

Duration of Dosing: 4 weeks (QW, 5 doses)

Report Number: 2015033-2

Sex			**Male**				**Female**			
Daily Dose (mg/kg)			**0 (Control)**	**5**	**30**	**150**	**0 (Control)**	**5**	**30**	**150**
Animal number			**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Tissue	**Abnormal**	**Degree**	**Observed animal number**							
Microscopic pathology (at the end of recovery phase)										
Injection site										
	Hemorrhage, subcutis	+	0	1	2	0	1	1	0	0
		++	0	1	0	0	0	1	1	0
		+++	2	0	0	2	0	0	0	1
	Infiltration, mononuclear	+	1	1	2	0	0	0	1	0
	cell, dermis/subcutis	++	1	1	0	1	1	0	0	0
	Infiltration, neutrophil,	++	0	1	0	1	1	0	0	0
	dermis/subcutis									
	Infiltration, mixed cell,	+	0	0	0	0	1	1	1	0
	dermis/subcutis	++	0	0	0	0	0	1	0	1
	Ulcer	+	0	0	0	1				
	Thrombus	++	0	0	0	0	1	0	0	0

No micropathology changes were observed in cerebrum, parathyroid(2), spinal cord(cervical, thoracic, lumbar), thymus, sternum with bonemarrow, aorta, tongue, trachea, esophagus, gall bladder, adrenal gland(2), stomach, duodenum, jejunum, ileum, cecum, colon, rectum, testis(2),epididymis(2), seminal vesicle, uterus (with cervix), oviduct, urinary bladder, sciatic never, mammary gland (female only), femur, eye(2), opticnever(2).

Notes: "-" no micropathology change, "+" minimal change, "++" mild change, "+++" moderate change, "++++" marked change. Parathroid missing: MD304, MD405, FD405. Prostate missing: MD104. One side of parathyroid missing: MD105, MD404, FD404.

17 Other Toxicity Studies

17.1 Tissue Cross-reactivity Study with Normal Cynomolgus Monkey Tissues

Test Article: KN035

Report Title: Tissue cross-reactivity with Cynomolgus monkey tissues

Species/Strain :

Cynomolgus monkey frozen tissue

Report Number:337-0003-IM

Date of First Dose: Aug. 18 2015

Location in CTD: M4.2.3.7.7.1

Special Features: The biotinylated KN035 was the specific primary antibody

GLP Compliance: Yes

Result: Specific staining was observed in the cytoplasm of the follicle epithelium of the thyroid at 25 μg/mL Biotin-KN035. No specific staining was observed in any other frozen Cynomolgus monkey tissues.

Tissue	Test Article (Biotin-KN035)		Control Article (Biotin-Human IgG1)		Reagent Control	Tissue Validation Control	Comments
	5 (μg/mL)	25 (μg/mL)	5 (μg/mL)	25 (μg/mL)	0.01 mol/L PBS	(CD31)	
Adrenal	0/3	0/3	0/3	0/3	0/3	Pos	-
Bladder	0/3	0/3	0/3	0/3	0/3	Pos	-
Blood cells	0/3	0/3	0/3	0/3	0/3	Pos	-
Bone marrow (femur)	0/3	0/3	0/3	0/3	0/3	Pos	-
Breast	0/3	0/3	0/3	0/3	0/3	Pos	-
Cerebellum	0/3	0/3	0/3	0/3	0/3	Pos	-
Colon	0/3	0/3	0/3	0/3	0/3	Pos	-
Endothelium (Aorta)	0/3	0/3	0/3	0/3	0/3	Pos	-
Eye	0/3	0/3	0/3	0/3	0/3	Pos	-
Fallopian tube	0/3	0/3	0/3	0/3	0/3	Pos	-
Small intestine (duodenum)	0/3	0/3	0/3	0/3	0/3	Pos	-
Heart	0/3	0/3	0/3	0/3	0/3	Pos	-
Kidney (glomerulus, tubule)	0/3	0/3	0/3	0/3	0/3	Pos	-
Liver	0[a]/3[b]	0/3	0/3	0/3	0/3	Pos	-

Test Article: KN035

Report Title: Tissue cross-reactivity with Cynomolgus monkey tissues

Species/Strain : **Report Number:**337-0003-IM

Cynomolgus monkey frozen tissue

Date of First Dose: Aug. 18 2015 **Location in CTD:** M4.2.3.7.7.1

Special Features: The biotinylated KN035 was the specific primary antibody **GLP Compliance:** Yes

Result: Specific staining was observed in the cytoplasm of the follicle epithelium of the thyroid at 25 μg/mL Biotin-KN035. No specific staining was observed in any other frozen Cynomolgus monkey tissues.

Tissue	Test Article (Biotin-KN035)		Control Article (Biotin-Human IgG1)		Reagent Control	Tissue Validation Control	Comments
	5 (μg/mL)	25 (μg/mL)	5 (μg/mL)	25 (μg/mL)	0.01 mol/L PBS	(CD31)	
Lung	0/3	0/3	0/3	0/3	0/3	Pos	-
Lymph node (mesenteric)	0/3	0/3	0/3	0/3	0/3	Pos	-
Ovary	0/3	0/3	0/3	0/3	0/3	Pos	-
Pancreas	0/3	0/3	0/3	0/3	0/3	Pos	-
Pituitary	0/3	0/3	0/3	0/3	0/3	Pos	-
Prostate	0/3	0/3	0/3	0/3	0/3	Pos	-
Skin	0/3	0/3	0/3	0/3	0/3	Pos	-
Spinal cord (thoracic)	0/3	0/3	0/3	0/3	0/3	Pos	-
Spleen	0/3	0/3	0/3	0/3	0/3	Pos	-
Stomach	0/3	0/3	0/3	0/3	0/3	Pos	-
Straited muscle(skeletal muscle)	0/3	0/3	0/3	0/3	0/3	Pos	-
Testis	0/3	0/3	0/3	0/3	0/3	Pos	-
Thymus	0/3	0/3	0/3	0/3	0/3	Pos	-
Thyroid	0/3	2+/occasional 3+/frequent 1+/rare	0/3	0/3	0/3	Pos	Follicle epitum,

Test Article: KN035

Report Title: Tissue cross-reactivity with Cynomolgus monkey tissues

Species/Strain :

Cynomolgus monkey frozen tissue

Report Number:337-0003-IM

Date of First Dose: Aug. 18 2015

Location in CTD: M4.2.3.7.7.1

Special Features: The biotinylated KN035 was the specific primary antibody

GLP Compliance: Yes

Result: Specific staining was observed in the cytoplasm of the follicle epithelium of the thyroid at 25 μg/mL Biotin-KN035. No specific staining was observed in any other frozen Cynomolgus monkey tissues.

Tissue	Test Article (Biotin-KN035)		Control Article (Biotin-Human IgG1)		Reagent Control	Tissue Validation Control	Comments
	5 (μg/mL)	25 (μg/mL)	5 (μg/mL)	25 (μg/mL)	0.01 mol/L PBS	(CD31)	
Tonsil	0/3	0/3	0/3	0/3	0/3	Pos	-
Ureter	0/3	0/3	0/3	0/3	0/3	Pos	-
Uterus (cervix)	0/3	0/3	0/3	0/3	0/3	Pos	-
Uterus (endometrium)	0/3	0/3	0/3	0/3	0/3	Pos	-

Note:
Positivity of staining (intensity): 1+=Weak, 2+=Moderate, 3+=Strong, 4+=Intense.
Pos=Positive,. "-"= not applicable
a = numbers of positive tissue slide, b = number of tissues examined (3 different donors)

17.2 Tissue Cross-reactivity Study with Human Tissues

Test Article: KN035

Report Title: Tissue cross-reactivity with human tissues

Species/Strain :

Normal human frozen tissues

Report Number:337-0002-IM

Date of First Dose: July 28, 2015

Location in CTD: M4.2.3.7.7.2

Special Features: The biotinylated KN035 was the specific primary antibody

GLP Compliance: Yes

Result: Specific staining was observed in the membrane of the trophoblastic cells in the placenta at both concentrations of biotinylated KN035, as well as in the cytoplasm of the follicle epithelium of the thyroid at 25 μg/mL of biotinylated KN035. No specific staining was observed in any other frozen human tissues stained with Biotin-HumanIgG1.

Tissue	Test Article (Biotin-KN035)		Control Article (Biotin-Human IgG1)		Reagent Control	Tissue Validation Control	Comments
	5 (μg/mL)	25 (μg/mL)	5 (μg/mL)	25 (μg/mL)	0.01 mol/L PBS	(CD31)	
Adrenal	0[a]/3[b]	0/3	0/3	0/3	0/3	Pos	Medulla not present Cortex and medulla not present
Endothelium (Aorta)	0/3	0/3	0/3	0/3	0/3	Pos	-
Bladder	0/3	0/3	0/3	0/3	0/3	Pos	-
Blood cell	0/3	0/3	0/3	0/3	0/3	Pos	-
Bone marrow	0/3	0/3	0/3	0/3	0/3	Pos	-
Cerebral cortex	0/3	0/3	0/3	0/3	0/3	Pos	-
Cerebellum	0/3	0/3	0/3	0/3	0/3	Pos	-
Pituitary	0/3	0/3	0/3	0/3	0/3	Pos	-
Breast	0/3	0/3	0/3	0/3	0/3	Pos	Mammary gland not present
Colon	0/3	0/3	0/3	0/3	0/3	Pos	-

Test Article: KN035

Report Title: Tissue cross-reactivity with human tissues

Species/Strain :

Normal human frozen tissues

Report Number:337-0002-IM

Date of First Dose: July 28, 2015

Location in CTD: M4.2.3.7.7.2

Special Features: The biotinylated KN035 was the specific primary antibody

GLP Compliance: Yes

Result: Specific staining was observed in the membrane of the trophoblastic cells in the placenta at both concentrations of biotinylated KN035, as well as in the cytoplasm of the follicle epithelium of the thyroid at 25 μg/mL of biotinylated KN035. No specific staining was observed in any other frozen human tissues stained with Biotin-HumanIgG1.

Tissue	Test Article (Biotin-KN035)		Control Article (Biotin-Human IgG1)		Reagent Control	Tissue Validation Control	Comments
	5 (μg/mL)	25 (μg/mL)	5 (μg/mL)	25 (μg/mL)	0.01 mol/L PBS	(CD31)	
Eye	0/3	0/3	0/3	0/3	0/3	Pos	-
Fallopian tube	0/3	0/3	0/3	0/3	0/3	Pos	-
Heart	0/3	0/3	0/3	0/3	0/3	Pos	-
Small intestine	0/3	0/3	0/3	0/3	0/3	Pos	Small intestine
Kidney（glomerulus，tubule）	0/3	0/3	0/3	0/3	0/3	Pos	-
Liver	0/3	0/3	0/3	0/3	0/3	Pos	-
Lung	0/3	0/3	0/3	0/3	0/3	Pos	-
Lymph node	0/3	0/3	0/3	0/3	0/3	Pos	-
Striated muscle	0/3	0/3	0/3	0/3	0/3	Pos	-
Ovary	0/3	0/3	0/3	0/3	0/3	Pos	-
Pancreas	0/3	0/3	0/3	0/3	0/3	Pos	-
Placeta	1+ Frequent 1+ Frequent Neg	2+ Frequent 2+ Frequent Neg	0/3	0/3	0/3	Pos	Trophoblastic cells, membrane
Prostate	0/3	0/3	0/3	0/3	0/3	Pos	-
Skin	0/3	0/3	0/3	0/3	0/3	Pos	Epidermis not

Test Article: KN035

Report Title: Tissue cross-reactivity with human tissues

Species/Strain :

Normal human frozen tissues

Report Number:337-0002-IM

Date of First Dose: July 28, 2015

Location in CTD: M4.2.3.7.7.2

Special Features: The biotinylated KN035 was the specific primary antibody

GLP Compliance: Yes

Result: Specific staining was observed in the membrane of the trophoblastic cells in the placenta at both concentrations of biotinylated KN035, as well as in the cytoplasm of the follicle epithelium of the thyroid at 25 μg/mL of biotinylated KN035. No specific staining was observed in any other frozen human tissues stained with Biotin-HumanIgG1.

Tissue	Test Article (Biotin-KN035)		Control Article (Biotin-Human IgG1)		Reagent Control	Tissue Validation Control	Comments
	5 (μg/mL)	25 (μg/mL)	5 (μg/mL)	25 (μg/mL)	0.01 mol/L PBS	(CD31)	
							present
Spinal cord	0/3	0/3	0/3	0/3	0/3	Pos	-
Spleen	0/3	0/3	0/3	0/3	0/3	Pos	-
Testis	0/3	0/3	0/3	0/3	0/3	Pos	-
Thymus	0/3	0/3	0/3	0/3	0/3	Pos	Lymphoid element not present
Thyroid	0/3	Neg 1+ Rare 2+ Occasional	0/3	0/3	0/3	Pos	Follicle epithelium, cytoplasm,
Tonsil	0/3	0/3	0/3	0/3	0/3	Pos	-
Ureter	0/3	0/3	0/3	0/3	0/3	Pos	Fat only, Smooth muscle only
Uterus cervix	0/3	0/3	0/3	0/3	0/3	Pos	Smooth muscle only

Test Article: KN035

Report Title: Tissue cross-reactivity with human tissues

Species/Strain :

Normal human frozen tissues

Report Number:337-0002-IM

Date of First Dose: July 28, 2015

Location in CTD: M4.2.3.7.7.2

Special Features: The biotinylated KN035 was the specific primary antibody

GLP Compliance: Yes

Result: Specific staining was observed in the membrane of the trophoblastic cells in the placenta at both concentrations of biotinylated KN035, as well as in the cytoplasm of the follicle epithelium of the thyroid at 25 μg/mL of biotinylated KN035. No specific staining was observed in any other frozen human tissues stained with Biotin-HumanIgG1.

Tissue	Test Article (Biotin-KN035)		Control Article (Biotin-Human IgG1)		Reagent Control	Tissue Validation Control	Comments
	5 (μg/mL)	25 (μg/mL)	5 (μg/mL)	25 (μg/mL)	0.01 mol/L PBS	(CD31)	
Uterus endometrium	0/3	0/3	0/3	0/3	0/3	Pos	Smooth muscle only

Note:
Positivity of staining (intensity): 1+=Weak, 2+=Moderate, 3+=Strong, 4+=Intense.
Neg=Negative, Pos=Positive,. "-"= not applicable
a = numbers of positive tissue slide, b = number of tissues examined (3 different donors)

17.3 *In Vitro* Hemolysis Test of KN035 with Rabbit Red Blood Cells

Test Article: KN035

Report Title: *In vitro* Hemolysis Test for KN035

Test System :

Rabbit red blood cells

Date of Blood Collection: Nov.18, 2015 **Date of Testing:**Nov.18, 2015 **Report Number:**2015046

Negative Control: 0.9% NaCl Injection **Concentration:** 196.78 mg/mL **Location in CTD:** M4.2.3.7.7.3

Positive Control: Sterile Water Injection (H_2O) **Vehicle/Formulation:**0.9% NaCl injection

GLP Compliance: Yes

Compound/Test Article		Indexes	15 min	30 min	45 min	1h	2h	3h
Test Article (KN035)	1	Hemolysis	-	-	-	-	-	-
		Aggregation	-	-	-	-	-	-
	2	Hemolysis	-	-	-	-	-	-
		Aggregation	-	-	-	-	-	-
	3	Hemolysis	-	-	-	-	-	-
		Aggregation	-	-	-	-	-	-
	4	Hemolysis	-	-	-	-	-	-
		Aggregation	-	-	-	-	-	-
	5	Hemolysis	-	-	-	-	-	-
		Aggregation	-	-	-	-	-	-
Test Article (KN035 buffer)	1	Hemolysis	-	-	-	-	-	-
		Aggregation	-	-	-	-	-	-
	2	Hemolysis	-	-	-	-	-	-
		Aggregation	-	-	-	-	-	-
	3	Hemolysis	-	-	-	-	-	-
		Aggregation	-	-	-	-	-	-
	4	Hemolysis	-	-	-	-	-	-
		Aggregation	-	-	-	-	-	-

Test Article: KN035

Report Title: *In vitro* Hemolysis Test for KN035

Test System :

Rabbit red blood cells

Date of Blood Collection: Nov.18, 2015 **Date of Testing:**Nov.18, 2015 **Report Number:**2015046

Negative Control: 0.9% NaCl Injection **Concentration:** 196.78 mg/mL **Location in CTD:** M4.2.3.7.7.3

Positive Control: Sterile Water Injection (H_2O) **Vehicle/Formulation:**0.9% NaCl injection

GLP Compliance: Yes

Compound/Test Article		Indexes	15 min	30 min	45 min	1h	2h	3h
	5	Hemolysis	-	-	-	-	-	-
		Aggregation	-	-	-	-	-	-
Negative Control	6	Hemolysis	-	-	-	-	-	-
(0.9% NaCl Injection)		Aggregation	-	-	-	-	-	-
Positive Control	7	Hemolysis	+	+	+	+	+	+
(H_2O)		Aggregation	-	-	-	-	-	-

Note: "-" indicates no hemolysis or no agglutination; "+" indicates complete hemolysis.

17.4 Studies of immunogenicity

17.4.1 Single dose immunogenicity study in Sprague Dawley Rat

Test Article: KN035

Report Title: Pharmacokinetics of KN035 in SD rat

Test System : Bridging ELISA method

Report Number: RDR-KN035-PD-2014-015
Location in CTD: M4.2.2.2.3
GLP Compliance: No

Group		Before dosing 0min	2.1 times as much as Mean OD of before dosing 0min	15d	28d
KN035 IP (10mg/kg)	**Female**	0*/5#	0.350	3/5	**5/5**
	Male	0/5	0.350	1/5	4/5

*: Numbers of animals with positive signal
#: total number of animals in this group

17.4.2 Single dose immunogenicity study in Cynomolgus monkeys (exploratory study)

Test Article: KN035

Report Title: Dosage Exploratory Pharmacokinetics of KN035 in Cynomolgus Monkeys

Test System : Bridging ELISA method

Report Number:RDR-KN035-PD-2015-011
Location in CTD:M4.2.2.2.1
GLP Compliance: No

Group		10d	14d	17d	24d	32d
KN035 SC (15mg/kg)	**No.1**	-	-	1*/1#	1/1	-
	No.2	-	-	-	0/1	1/1
KN035SC (30mg/kg)	**No.3**	-	-	1/1	1/1	-
	No.4	-	-	0/1	0/1	0/1
KN035IV (15mg/kg)	**No.5**	-	-	0/1	1/1	-
	No.6	1/1	1/1	-	1/1	-

-: Not test
*: Numbers of animals with positive signal
#: total number of animals in this group

17.4.3 Single dose immunogenicity study in Cynomolgus monkeys

Test Article: KN035

Report Title: Test Report of Anti-KN035 Antibodies in Cynomolgus Monkey Serum(Study N2015042)

Test System : Bridging ELISA method

Report Number: N2015042Appendix 1
Location in CTD: M4.2.2.2.2
GLP Compliance: No

Group	9d	17d	28d	37d
KN035IVroutinegroup（15mg/kg）	1*/6#	1/6	4/6	6/6
KN035 SC routine group（5mg/kg）	1/6	5/6	5/6	5/6
KN035SC routine group（15mg/kg）	1/6	2/6	4/6	4/6
KN035SC routine group（50mg/kg）	0/6	0/6	0/6	0/6

*: Numbers of animals with positive signal
#: total number of animals in this group

17.4.4 Repeat dose immunogenicity studies in Cynomolgus monkeys

Test Article: KN035

Report Title: Test Report of Anti-KN035 Antibodies in Cynomolgus Monkey Serum(Study 2015033)

Test System : Bridging ELISA method

Report Number:2015033-2* Appendix V
Location in CTD: M4.2.3.2.1

GLP Compliance: No

Group	Two doses	Four doses	Recovery 4 weeks
KN035 SC dose（5mg/kg）	3*/10#	4/10	3/4
KN035 SC dose（30mg/kg）	1/10	0/10	0/4
KN035 SC dose（150mg/kg）	0/10	0/10	0/10

*: Numbers of animals with positive signal
#: total number of animals in this group