

Study Summary

Pregnant SD rats (22/group for main study and 12/dose for TK) were treated with combination of saxagliptin/metformin dose of 5/200 and 25/200 mg/kg/d from gestation day (GD) 6 through 15. There were no separate arms for saxagliptin or metformin in the study. Saxagliptin was prepared in 0.125% Avicel/water (1 ml/kg) while metformin was prepared in water (4 ml/kg) for oral gavage delivery. Blood samples for hematology and clinical chemistry and TK were collected from the TK group on GD 14-15. The combination saxagliptin/metformin was well tolerated and there were no deaths. There were no adverse findings or malformations at 5/200 mg/kg/d of saxagliptin/metformin (20x/4x the maximum therapeutic dose of saxagliptin/metformin, based on AUC). However, at higher dose of saxagliptin (25/200 mg/kg/d dose of saxagliptin/metformin), neural tube defect was observed in 2 fetuses from one litter. Neural tube defect also known as craniorachischisis was marked by incomplete closure of the skull and spinal column. The same two fetuses had missing renal papilla(e), microcaudia (short tail), and one of them had cleft palate. The fetal and litter incidence of craniorachischisis was 0.7% and 4.5%, respectively, which greatly exceeds historical experience. Two additional fetuses from a second litter showed an increased incidence of missing or absent digits of the paws/hindlimbs. The cause of malformation in the combination study is not clear since both drugs were not teratogenic in embryofetal development studies in rats and rabbits. Since malformations were seen when the dose of saxagliptin was raised from 5 to 25 mg/kg/d with no change in metformin dose, the data implicate saxagliptin as the potential cause of malformations, possibly via a pharmacodynamic interaction with metformin. However, the sponsor believes that malformations were due to metformin since at least in one publication, 500 mg/kg/d of metformin produced an incidence of neural tube defect (craniorachischisis) in pregnant rats (GD 1 to 12). The author of the paper had considered metformin not to be strongly teratogenic. The sponsor also stated that metformin treated patients have been shown to have low circulating levels of folate and Vit B12, two cofactors needed for synthesis of methionine. Since methionine is essential for normal fetal development, the malformations in the combination study were likely due to metformin and not saxagliptin. Spontaneous incidence of craniorachischisis is very rare. According to the sponsor the historical control data collected from 2005 to 2007 found only one incidence of craniorachischisis. This low historical background further highlights the need for repeating the study in rats as well as a new study in rabbits. The study should include separate arms for saxagliptin and metformin in addition to the combination. The sponsor has agreed to do the studies but the results of the two studies are likely to become available post approval (late 2009).

Historical control Data from

**HISTORICAL CONTROL DATA
RAT - CD@ IGS (CrI:CD[SD]), 1996-2007**

b(4)

ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES		
FETAL FINDINGS - SUMMARY DATA		
Parameter	Minimum	Maximum
GESTATION DAY 20		
Fetal Weight (G) - Males	3.49	4.21
Fetal Weight (G) - Females	3.28	3.93
Fetal Weight (G) - Total	3.38	4.11
GESTATION DAY 21		
Fetal Weight (G) - Males	5.02	6.14
Fetal Weight (G) - Females	4.80	5.82
Fetal Weight (G) - Total	4.94	5.97
COMBINATION OF GESTATION DAY 20 AND 21		
Major Malformations - Litters Affected (%)	0.0	13.6
Major Malformations - Fetuses Affected (%)	0.0	1.0
Minor External and Visceral Anomalies - Litters Affected (%)	0.0	33.3
Minor External and Visceral Anomalies - Fetuses Affected (%)	0.0	4.4
GESTATION DAY 20		
Minor Skeletal Anomalies - Litters Affected (%)	27.3	95.8
Minor Skeletal Anomalies - Fetuses Affected (%)	6.6	50.0
Vertebral Centrum Variants - Fetuses Affected (%)	9.7	40.7
Sternebral Variants 1 to 4 - Fetuses Affected (%)	1.3	26.9
Sternebral Variants 5 and 6 - Fetuses Affected (%)	49.9	96.7
GESTATION DAY 21		
Minor Skeletal Anomalies - Litters Affected (%)	45.5	95.0
Minor Skeletal Anomalies - Fetuses Affected (%)	9.3	46.7
Vertebral Centrum Variants (unossified, incomplete ossification, bipartite, semi-bipartite) - Fetuses Affected (%)	1.1	39.1
Sternebral Variants 1 to 4 (unossified, incomplete ossification, bipartite, semi-bipartite) - Fetuses Affected (%)	0.0	2.5
Sternebral Variants 5 and 6 (unossified, incomplete ossification, bipartite, semi-bipartite) - Fetuses Affected (%)	5.1	45.8

**HISTORICAL CONTROL DATA
RAT - CD@ IGS (Cr:CD/SD). 1996-2007**

b(4)

ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MAJOR MALFORMATIONS AND MINOR ANOMALIES				
	Litters examined		Total no. of studies used	
	EXTERNAL (EXT)	1814		82
VISCERAL (VIS)	1813			
SKELETAL (SKE)	1812			
TECHNIQUE OF WILSON (WT)	1812			
MAJOR MALFORMATIONS (TOTAL)	Litters affected			
	SUM	AVERAGE %	MIN %	MAX %
	37	2.09	0.00	13.64
Cranium: Auditory/vestibular system; absent (WT)	1	0.06	0.00	4.00
Cranium: Auditory/vestibular system; reduced/ incomplete formation (WT)	2	0.11	0.00	4.76
Cranium: Cleft palate/lip (EXT,WT)	3	0.17	0.00	4.76
Cranium: Microtia (EXT)	1	0.06	0.00	4.76
Cranium: Microcephaly (EXT,WT)	2	0.11	0.00	5.26
Cranium: Exencephaly (EXT,SKE)	1	0.06	0.00	5.00
Brain: Hydrocephaly (EXT,WT)	4	0.22	0.00	9.09
Brain: Cerebrum, cyst-like formation (WT)	1	0.06	0.00	4.00
Brain: Lateral ventricles reduced (WT)	1	0.06	0.00	4.00
Eye(s): Anophthalmia (EXT,WT)	6	0.33	0.00	5.26
Eye(s): Exophthalmia (EXT,WT)	1	0.06	0.00	4.00
Eye(s): Microphthalmia (WT)	2	0.11	0.00	4.00
Eye(s): Open (EXT,WT)	1	0.06	0.00	4.00
Eye(s): Retinal folding (WT)	2	0.11	0.00	4.35
Eye(s): Aphakia (WT)	1	0.06	0.00	4.35
Face: Aglossia (EXT,WT)	3	0.17	0.00	8.33
Face: Agnathia (EXT,WT)	5	0.28	0.00	8.33
Face: Astomia (EXT,WT)	3	0.17	0.00	5.26
Face: Micrognathia (EXT,WT)	1	0.06	0.00	4.17
Face: Mandibular micrognathia (EXT)	5	0.28	0.00	5.00
Face: Microstomia (EXT,WT)	1	0.06	0.00	4.00
Face: Nares; reduced (EXT,WT)	1	0.06	0.00	4.00
Face: Nares opening; reduced (WT)	1	0.06	0.00	4.17
Face: Nasal septum/turbinate formation; reduced (WT)	1	0.06	0.00	4.17
Face: Nasal septum; lack of turbinate formation (WT)	1	0.06	0.00	4.76
Face: Palate; absent (WT)	3	0.17	0.00	8.33
Face: Split tongue (WT)	1	0.06	0.00	4.76
Face: Upper jaw absent (EXT)	2	0.11	0.00	5.26
Face: Nares absent (EXT)	1	0.06	0.00	5.26
Face: Probosis (EXT,WT)	1	0.06	0.00	5.26
Heart: Interventricular septal defect (VIS)	2	0.11	0.00	5.00
Heart: Dilatation of ascending aorta (VIS)	1	0.06	0.00	4.17
Heart: Right descending aorta (VIS)	1	0.06	0.00	5.00

HISTORICAL CONTROL DATA
DATE: 03/10/05 (C) J. G. GIBSON, 1995-2007

ALL ROUTES OF ADMINISTRATION

b(4)

EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS				
MAJOR MALFORMATIONS AND MINOR ANOMALIES				
MAJOR MALFORMATIONS (CONT'D)	Litters affected			
	SUM	AVERAGE %	MIN %	MAX %
Heart: Stenosis of ascending aorta (VIS)	1	0.06	0.00	5.00
Heart: Transposition of major vessels (VIS)	4	0.22	0.00	5.00
Heart: Globular heart (VIS)	1	0.06	0.00	5.00
Heart: Ringed aorta (VIS)	1	0.06	0.00	4.76
Diaphragm: Diaphragmatic hernia (VIS)	1	0.06	0.00	4.35
Lungs and thymus: Lung lobes; absent (VIS)	2	0.11	0.00	4.76
Lungs and thymus: Lung lobes; reduced (VIS)	1	0.06	0.00	4.76
Vertebral column: Multiple fusion and anomalies in vertebral column (SKE)	3	0.17	0.00	4.35
Thorax: Trunk shortened (EXT)	1	0.06	0.00	4.35
Abdomen: Anal atresia (EXT, VIS)	4	0.22	0.00	4.55
Abdomen: Gastroschisis (EXT)	1	0.06	0.00	4.00
Abdomen: Situs inversus (VIS)	1	0.06	0.00	5.00
Abdomen: Omphalocele (EXT)	5	0.28	0.00	5.00
Abdomen: Urogenital region fissure (EXT)	1	0.06	0.00	4.76
Abdomen: Abdominal muscles herniated (EXT)	1	0.06	0.00	4.17
Abdominal cavity: Colon blind (VIS)	1	0.06	0.00	4.00
Abdominal cavity: Malposition stomach/pancreas/spleen (VIS)	1	0.06	0.00	5.00
Abdominal cavity: Intestine; stenosis (VIS)	1	0.06	0.00	4.55
Tail: Acaudia (EXT)	2	0.11	0.00	4.00
Tail: Microcaudia (EXT)	4	0.22	0.00	4.76
Limb(s): Ectrodactyly (EXT)	2	0.11	0.00	4.76
Limb(s): Brachydactyly (EXT)	2	0.11	0.00	4.76
Limb(s): Abnormal flexure of hindlimb(s) (EXT)	2	0.11	0.00	4.76
Limb(s): Hindpaw(s) absent (SKE)	1	0.06	0.00	4.00
Skull: Mandible shortened (SKE)	1	0.06	0.00	5.00
Skull: Maxilla shortened/incisive bone (SKE)	1	0.06	0.00	5.00
Gross exam: Anasarca (EXT)	5	0.28	0.00	9.52
General: Situs inversus (VIS)	4	0.22	0.00	4.55
MINOR VISCERAL AND EXTERNAL ANOMALIES (TOTAL)	132	7.22	0.00	33.33
Cranium: Pinna(e); displaced (EXT)	1	0.06	0.00	4.17
Cranium: Subcutaneous hematoma (WT)	1	0.06	0.00	4.17
Cranium: Cutis aplasia (EXT, WT)	1	0.06	0.00	4.00
Cranium: Cyst-like formation subcutaneously (WT)	1	0.06	0.00	4.00
Cranium: Moderate dilatation of the third ventricle (WT)	3	0.17	0.00	4.55
Cranium: Moderate dilatation of the lateral ventricles (WT)	1	0.06	0.00	4.55
Eye(s): Lens(es) oval (WT)	8	0.44	0.00	9.52
Eye(s): Hematoma adjacent to eye(s) (WT)	2	0.11	0.00	5.00
Face: Protruding tongue (EXT)	1	0.06	0.00	5.00
Nasal septum: Reduction in turbinate formation (WT)	1	0.06	0.00	4.00
Heart: Innominate artery absent (VIS)	13	0.72	0.00	10.53
Heart: Innominate artery reduced (VIS)	1	0.06	0.00	5.00
Heart: Innominate artery malpositioned (VIS)	1	0.06	0.00	4.76
Liver: Discoloration pale (VIS)	1	0.06	0.00	4.17
Liver: Supernumerary lobes (VIS)	7	0.39	0.00	10.00
Liver: Vestigial lobe (VIS)	1	0.06	0.00	5.00
Spleen: Small (VIS)	1	0.06	0.00	4.55
Kidney(s): Reduction of renal papilla(e) (VIS)	9	0.50	0.00	16.67
Kidney(s): Reduced (VIS)	2	0.11	0.00	5.00
Ureter(s): Dilatation (VIS)	69	3.81	0.00	27.27
Ureter(s): Megaureter (VIS)	22	1.21	0.00	13.64
Adrenal gland(s): Hemorrhage (VIS)	1	0.06	0.00	4.76
Testes: Malpositioned (VIS)	1	0.06	0.00	4.76
Skin: Pale (EXT)	1	0.06	0.00	4.17
Tail: Kinked (EXT)	3	0.17	0.00	4.55
General: Subcutaneous hematoma (EXT)	2	0.11	0.00	8.00

HISTORICAL CONTROL DATA
 RAT - CD@ IGS (CrI:CDISD). 1996.2007

ALL ROUTES OF ADMINISTRATION
 GESTATION DAY 20*

b(4)

EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MAJOR MALFORMATIONS AND MINOR ANOMALIES				
SKELETAL (SKE)	Litters examined	Total no. of studies used		
	806	36		
MINOR SKELETAL ANOMALIES (TOTAL)	Litters affected			
	SUM	AVERAGE %	MIN %	MAX %
	619	76.80	27.27	95.83
SKULL				
Frontal bone(s): Reduced ossification	5	0.62	0.00	5.26
Frontal bone(s): Irregular ossification	1	0.12	0.00	4.17
Parietal bone(s): Reduced ossification	52	6.45	0.00	23.81
Parietal bone(s): Irregular ossification	5	0.62	0.00	9.09
Supraoccipital bone: Reduced ossification	110	13.65	0.00	42.86
Supraoccipital bone: Irregular ossification	121	15.01	0.00	55.00
Interparietal bone: Reduced ossification	170	21.09	0.00	77.27
Interparietal bone: Irregular ossification	224	27.79	0.00	75.00
Hyoid bone: Absent	6	0.74	0.00	9.52
Hyoid bone: Reduced ossification	365	45.29	0.00	80.00
Hyoid bone: Irregular ossification	4	0.50	0.00	12.50
Extra suture(s) in frontal/parietal bone(s)	1	0.12	0.00	4.00
VERTEBRAL COLUMN				
Extra pre-sacral vertebra(e)	7	0.87	0.00	5.00
25 pre-sacral vertebrae	6	0.74	0.00	10.53
Lumbar centrum: Bipartite	1	0.12	0.00	4.17
Lumbar centrum: Semi-bipartite	6	0.74	0.00	8.33
Lumbar vertebral centrum: Absent	1	0.12	0.00	4.76
Lumbar vertebral arch(es): Reduced ossification	1	0.12	0.00	5.00
Lumbar vertebral arch(es): Irregular ossification	0	0.00	0.00	0.00
Ossification center on 1st lumbar vertebra or 14th thoracic vertebra	170	21.09	4.17	50.00
Sacral vertebra(c): Reduced no.	1	0.12	0.00	4.17
Sacral vertebral centrum: Absent	2	0.25	0.00	4.76
Sacral vertebral centrum: Reduced ossification	3	0.37	0.00	5.26
Sacral vertebral arch(es): Reduced ossification	23	2.85	0.00	24.00
Caudal vertebra(e): Reduced no.	12	1.49	0.00	5.26
Thoracic centrum: Misaligned	1	0.12	0.00	4.76
Thoracic centrum: Reduced ossification	2	0.25	0.00	4.55
Thoracic vertebral centra: Misaligned	1	0.12	0.00	4.17
Thoracic vertebral centrum: Displaced	2	0.25	0.00	4.55
Thoracic vertebral arch(es): Fused	1	0.12	0.00	4.17
Thoracic vertebral arch(es): Absent	2	0.25	0.00	4.55
Thoracic vertebral arch(es): Reduced ossification	1	0.12	0.00	4.17

* = Last study conducted in 2003

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