[4/18/2008(Fri) 10:00~10:35/1st FL)]

LC15-0133, a DPP IV Inhibitor: Efficacy in Various Animal Models

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GLP-1-based drugs (GLP-1 analogues and DPP IV inhibitors) and incretin mimetics are currently one of the most exciting classes of agents for type II diabetes. GLP-1, a gut peptide, is an incretin that potentiates glucose-dependent insulin release from the pancreas, slows GI-transit and stimulates the proliferation of beta-cells. DPP IV inhibitors act like incretins by inhibiting DPP IV which inactivates GLP-1. LC15-0133 is a competitive, reversible DPP IV inhibitor (IC_{50} = 24 nM, Ki=0.247 nM) with excellent selectivity over other critical human proteases such as DPP II, DPP 8, elastase, trypsin, and urokinase. LC15-0133 showed long half-life and good bioavailability in rats and dogs. Inhibition of plasma DPP IV activity by LC15-0133 was kept more than 50% 24 hours after oral dosing in rats and dogs at 0.1 mg/kg and 0.02 mg/kg, respectively. The Minimum effective doses of LC15-0133 were 0.01 mg/kg for lowering blood glucose excursion during oral glucose tolerance test and 0.1 mg/kg for increasing glucose-induced GLP-1 response in C57BL/6 mice. Repeat oral administration of LC15-0133 for 1 month delayed the progression to diabetes and reduced HbA1c levels in a dose-dependent manner in Zucker Diabetic Fatty rats. In conclusion, LC15-0133 is a novel, potent, selective and orally active DPP IV inhibitor and showed an excellent blood glucose lowering effects in various animal models.

LC15-0133, DPP IV 저해제: 여러 동물 모델에서의 효능

임현주, 약학박사

LG 생명과학 기술 연구원, 대덕 연구 단지, 대전

GLP 1 기반의 약(GLP-1 유도체와 DPP IV 저해제)과 인크레틴 유사체는 최근 가장 각광을 받는 2형 당뇨 치료제 계열 중 하나이다. GLP-1은 위장에서 분비되는 펩타이드 인크레틴 호르몬으로서 췌장으로부터의 당-의존적 인슐린 분비를 증진하고, 위장통과를 지연시키며, 췌장 베타세포의 증식을 촉진한다. DPP IV 저해제는 GLP-1을 불활성화시키는 DPP IV 효소의 활성을 저해함으로써 인크레틴처럼 작용한다. LC15-0133은 경쟁적, 가역적 DPP IV 저해제 (IC_{50} = 24 nM, Ki=0.247 nM)이며, DPP II, DPP 8, 엘라스타제, 트립신, 유로키나제에 비해 DPP IV 에 대한 선택적 억제 효능이 우수하다. LC15-0133은 랫과 개에서 긴 반감기와, 우수한 경구흡수율을 보였다. LC15-0133는 랫과 개에서 각각 0.1 mg/kg과 0.02 mg/kg 용량으로 경구투여하고 24시간이 지난 후에도 50%이상의 혈장 DPP IV 활성 억제 효능을 유지하였다. C57BL/6 마우스에서 LC15-0133이 경구당부하에 의한 혈당증가를 억제하는 최소유효용량은 0.01 mg/kg, 당에 의한 GLP-1 분비를 증가시키는 최소유효용량은 0.1 mg/kg 이다. Zucker 당뇨 랫에서 LC15-0133의 1개월간의 경구반복투여는 당뇨병으로의 진행을 지연시키고, 혈중 HbA1c를 감소시켰다. 결론적으로, LC15-0133은 신규의 강력하고, 선택적인 경구 DPP IV 저해제이며, 여러 가지 동물모델에서 탁월한 혈당강하효능을 보였다.

LC15-0133, a DPP IV Inhibitor: Efficacy in Various Animal Models

임 현 주

2008. 04. 18

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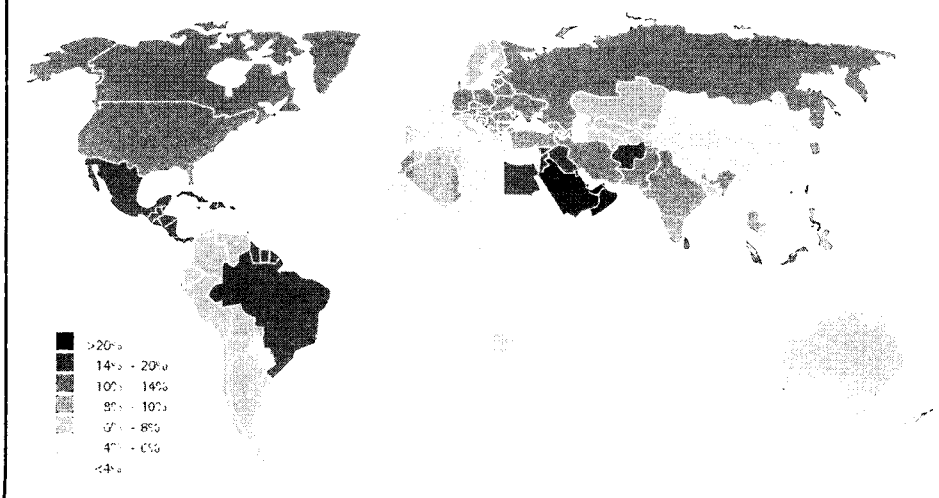
Epidemic Diabetes

Prevalence estimates of diabetes, 2025



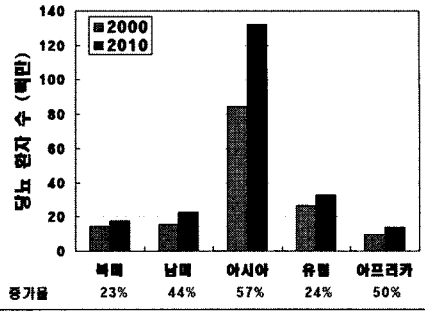
SOURCE: DIABETES ATLAS, 3RD EDITION - INTERNATIONAL DIABETES FEDERATION, 2006

당뇨병 치료제 시장

당뇨환자 증가

국내
- 10명중 1명이 당뇨환자
- 60세 이상 10명 중 2명
- 내당능 장애 환자 증가
  → 2030년 700만명

세계
- 2003년 1억 9400만명
- 2010년 2억 2000만명 예상



막대한 시장
2012년 DPPIV 억제제 시장 23억불[1]

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[1] Datamonitor, 2006

신규 당뇨병 치료제 개발의 필요성

기존 당뇨병 치료제의 문제점

Sulfonylurea계 Glibenclamide, Glipizide	저혈당, 인슐린 분비능 상실
Biguanide계 Metformin	위장장애, 신장독성
α-Glucosidase 저해제 Miglitol, Voglibose	설사, 복통
Glitazone계 Pioglitazone, Rosiglitazone	심부전, 빈혈, 체중증가
Meglitinide계 Repaglinide, Nateglinide	저혈당, 두통, 설사, 관절통

획기적/근본적 치료제 개발 필요
"DPP IV Inhibitor"

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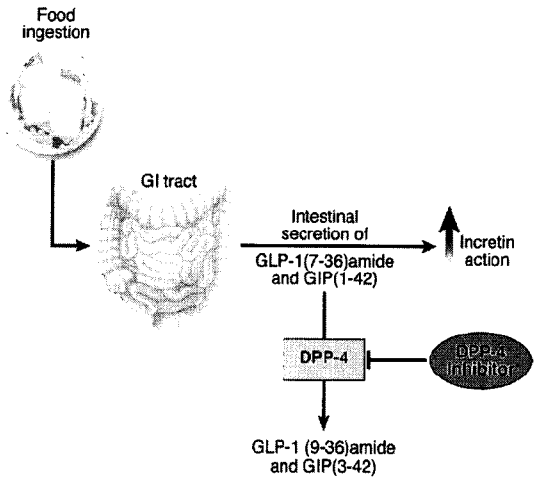
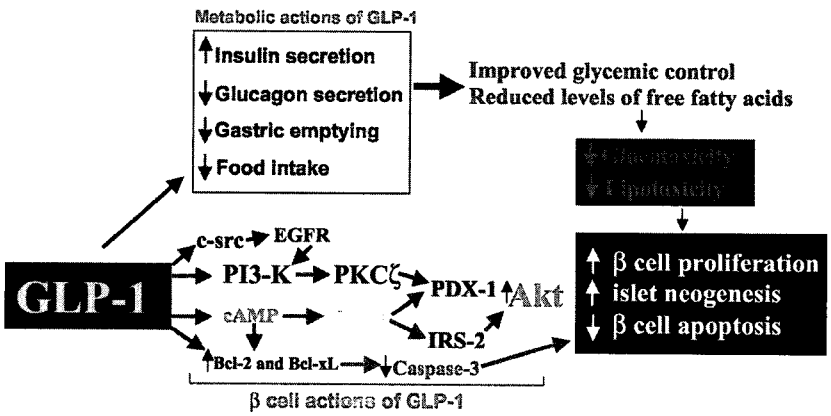
Mechanism of Action



LG Life Sciences Source: L. BAGGIO and D. DRUCKER, GASTROENTEROLOGY 2007;132:2131–2157

Mechanism of Action

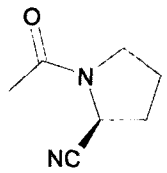


DPP IV Inhibition: Blood Glucose Control+ α

LG Life Sciences Source: Drucker, D. J. Endocrinology 2003;144:5145-5148

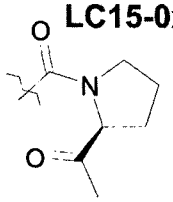
LGLS DPP IV Inhibitors

DPP IV 억제제로
개발중인 당뇨 치료제



약효
약효시간
약동력학
월등 개선

LC15-0xxx



Novel Heterocycle

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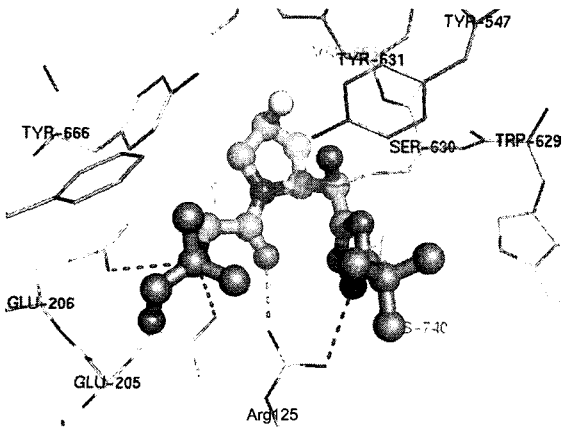
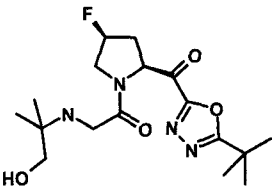
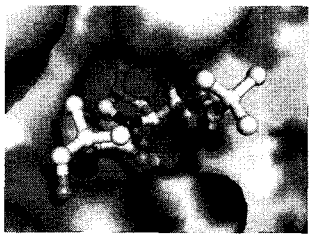
Crystal Structure: DPP IV & LC15-0133 Complex







Unique Tight Binding

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In vitro Activity & Selectivity

	IC_{50} (uM)
DPP IV	0.024
DPP II	145.8
DPPVIII	1.15
Elastase	227.8
Trypsin	>400
Urakinase	>400

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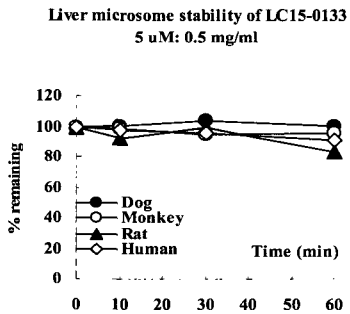
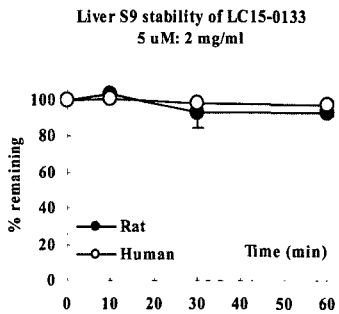
in vitro Metabolism: Microsome & S9





모든 종에 대한 대사 안정성

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Plasma Protein Binding

Protein binding (%) in plasma at 10 ug/mL

	Rat	Monkey	Human
LC15-0133	18.3	24.1	33.0

Low Protein Binding

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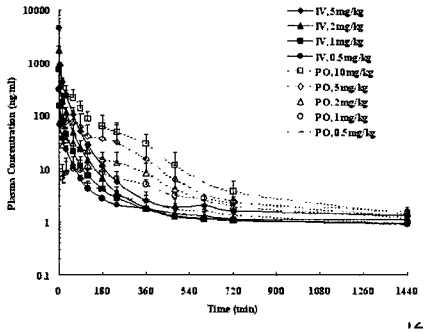
Rat Dose Dependency Study

(LLOQ = 1ng/ml)

Dose (mg/kg)	0.5		1		2		5		10	
N	5		5		7		6		4	
PO	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cmax (㎍/㎖)	0.011	0.004	0.013	0.006	0.043	0.014	0.122	0.056	0.280	0.105
Tmax (min)	48	16	108	54	81	77	130	140	30	21
AUCInfinity (㎍ min/㎖)	--	--	--	--	9.48	1.64	18.97	3.30	39.80	10.84
AUClast (㎍ min/㎖)	2.66	0.78	5.26	0.95	8.79	1.33	18.07	3.47	38.70	11.23
$T_{1/2elim}$(min)	--	--	--	--	405	170	534	441	567	257
AUClast/Dose	5.33	1.57	5.26	0.95	4.40	0.67	3.61*	0.69	3.87	1.12
BAinf(%)	--	--	--	--	48.5	11.3	43.9	9.1	45.7	6.9
BAlast(%)	59.4	25.5	63.6	17.5	47.5	9.9	44.3	10.7	47.1	7.9

*p<0.05 compared to 0.5 mpk, p<0.01 compared to 1mpk

Dose (mg/kg)	0.5		1		2		5	
N	5		7		11		9	
IV	Mean	SD	Mean	SD	Mean	SD	Mean	SD
t1/2 (min)	--	--	789	636	966	765	762	601
AUC_{last} (㎍ min/㎖)	4.71	0.81	8.02	1.48	17.75	2.62	40.78	4.19
$AUC_{Infinity}$ (㎍ min/㎖)	--	--	9.22	2.34	19.27	2.89	42.26	4.37
Vdβ (ml/kg)	--	--	113219	65535	141608	107656	129521	99150
CL(ml/min/kg)	--	--	114	25	106	15	119	13
MRT (min)	--	--	386	393	321	388	149	156
Vdss (ml/kg)	--	--	36495	29354	32122	38049	17399	17620



long half life and good bioavailability

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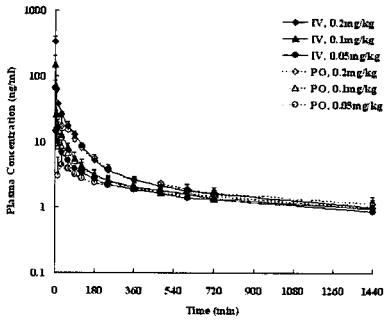
Dog Dose Dependency Study

Dose (mg/kg)	0.05		0.1		0.2	
N	3		3		3	
PO	Mean	SD	Mean	SD	Mean	SD
Cmax (㎍/㎖)	0.0044	0.0018	0.0099	0.0027	0.0195	0.0041
Tmax (min)	25	9	25	9	35	23
AUCinfinity (㎍ min/㎖)	4.06	1.08	4.75	1.13	6.33	1.38
AUClast (㎍ min/㎖)	2.43	0.67	2.81	0.59	4.27	0.43
$T_{1/2\,ep}$(min)	1145	116	1374	290	1205	269
BAinf(%)	93.5	15.9	88.6	13.4	80.6	13.0
BAlast(%)	86.7	15.9	75.1	5.9	68.1	7.0

Dose (mg/kg)	0.05		0.1		0.2	
N	3		3		3	
IV	Mean	SD	Mean	SD	Mean	SD
t1/2 (min)	1227	63	1185	73	1051	197
AUC_{last} (㎍ min/㎖)	2.79	0.33	3.72	0.50	6.28	0.33
$AUC_{infinity}$ (㎍ min/㎖)	4.30	0.41	5.35	0.78	7.84	0.81
Vdβ (ml/kg)	20775	2853	32290	3745	38558	3835
CL(ml/min/kg)	11.70	1.05	18.97*	2.86	25.71**	2.68
MRT (min)	1418	93	1209	53	797	244
Vdss (ml/kg)	16642	2460	22837	2443	20109	4262

*p<0.05 compared to 0.05mpk

**p<0.01 compared to 0.05mpk, p<0.05 compared to 0.1mpk



long half life and excellent bioavailability

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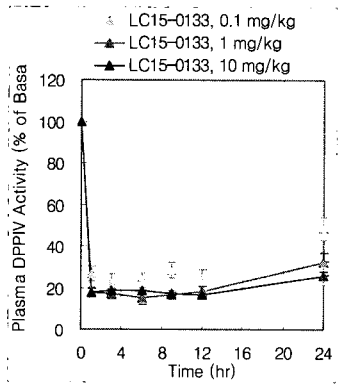
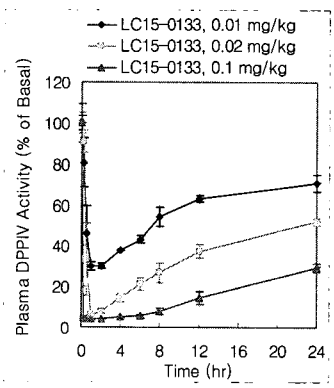
Plasma DPP IV Inhibition in Rats & Dogs



Animal: male SD Rats, n=3



Animal: female Beagle Dogs, n=2

excellent potency & long duration of action

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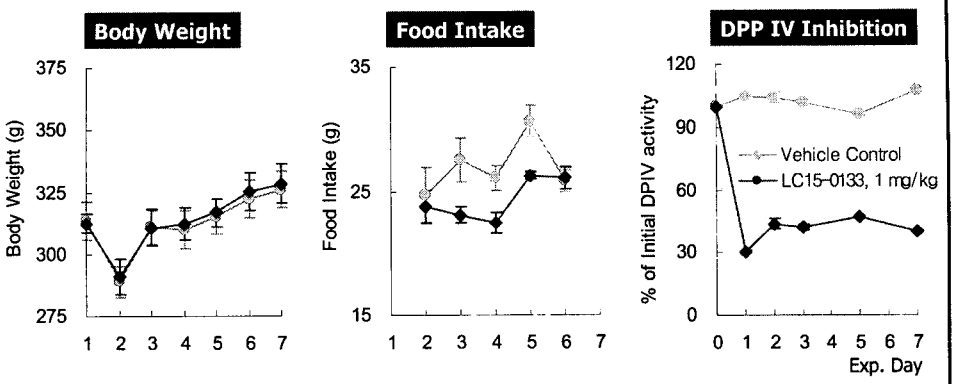
7-Day Repeat Dosing in SD Rats



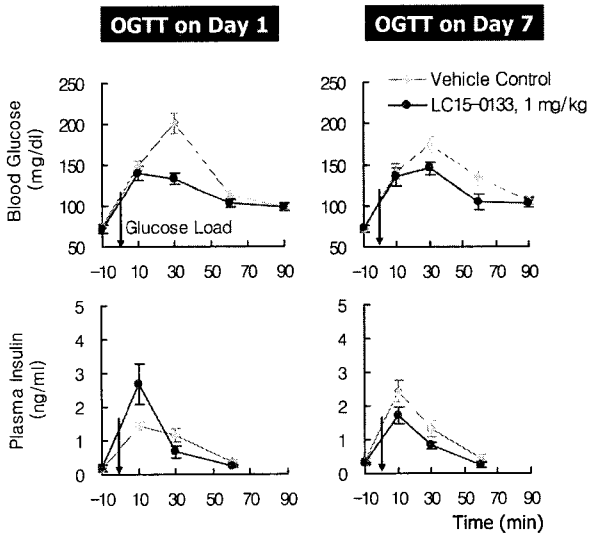
Animal
Male Sprague-Dawley Rats
5 animals/group
9 weeks old

Treatment
oral gavage
once daily

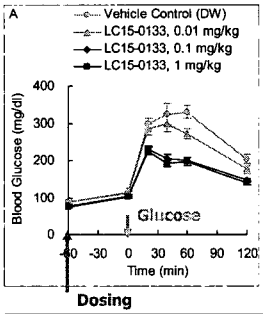
7-Day Repeat Dosing in SD Rats

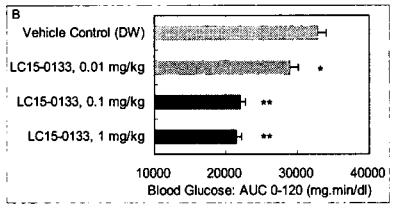
Animal
Male Sprague-Dawley Rats
5 animals/group
9 weeks old

OGTT
Trt: 22 hr after the last dose
15 hr fasting before OGTT
Glucose load: 1 g/kg



Acute Effects in C57BL/6 Mice



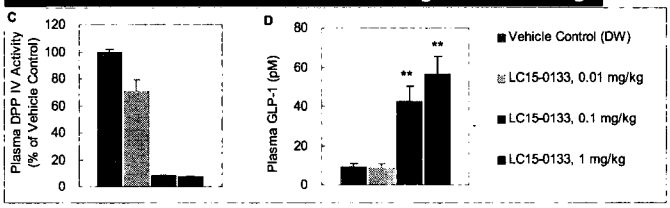


➢Animal
Male C57BL/6 mice
5~6 animals/group
26 weeks old

➢OGTT
Dosing: 1 hr before OGTT
Glucose load: 4 g/kg

• MED for lowering glucose excursion: 0.01 mg/kg
• MED for glucose induced GLP-1 increase: 0.1 mg/kg

Plasma DPP IV & GLP-1: 10 min after glucose loading



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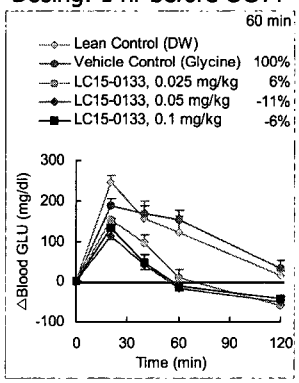
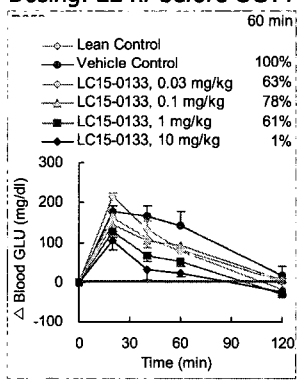
Acute Effects in DIO Mice

Dosing: 1 hr before OGTT



Animals: 21 weeks old, n=5
*Lean Control - age matched lean mice

Dosing: 22 hr before OGTT



Animals: 42 weeks old, n=5~7
* Lean Control - age matched lean mice

LC15-0133 exhibits prolonged efficacy 22 hours after oral dosing

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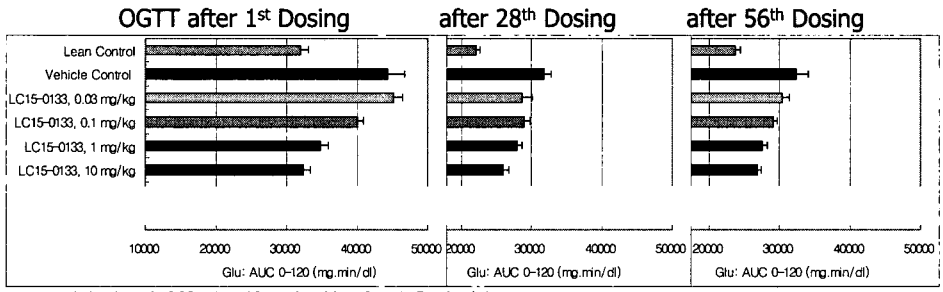
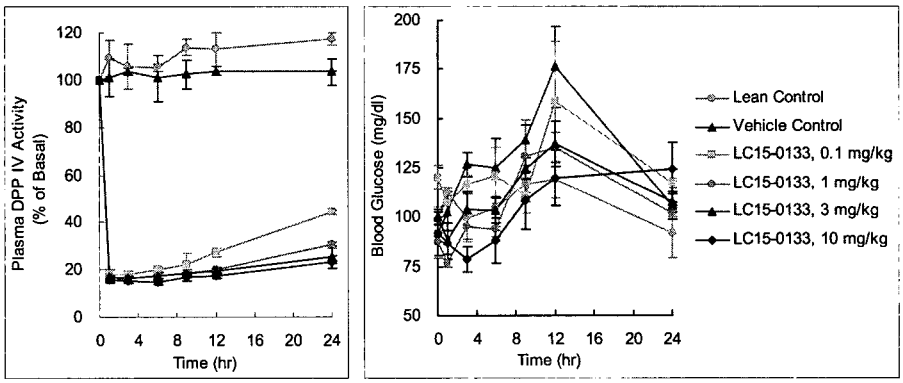
Chronic Effects in DIO Mice

Treatment: qd X 56, oral gavage
OGTT: 22 hrs after the last dosing



Animal: male DIO mice, 18 weeks old on Day 1, 5 animals/group
Dosing: once daily, oral gavage
Vehicle: 100 mM glycine HCl buffer

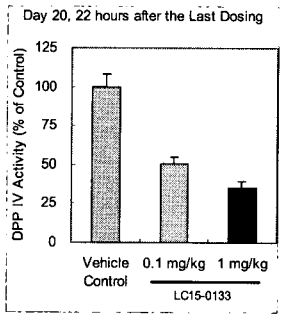
Acute Effects in Zucker Fatty Rats



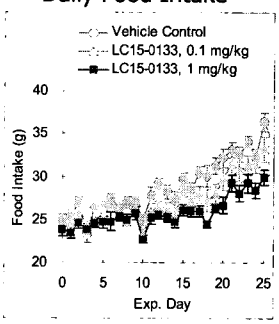
lean and fatty male Zucker Rats (Harlan, USA): 11 weeks old (n=2~3)

Chronic Effects in Zucker Diabetic Fatty Rats

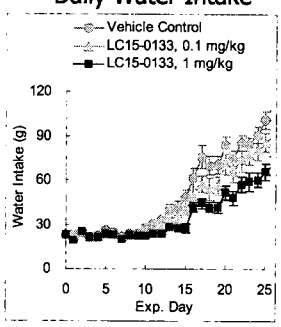
Plasma DPPIV



Daily Food Intake



Daily Water Intake



Animal: male Zucker Diabetic Fatty Rats, 6 weeks old on Day 1, n=8
Dosing: once daily, oral gavage
Vehicle: 100 mM glycine HCl buffer

LC15-0133 delayed the progression of diabetic symptoms in the male ZDF Rats

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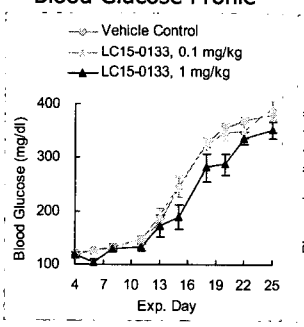
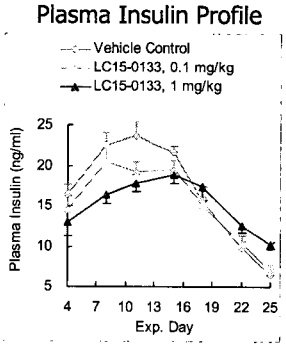
Chronic Effects in Zucker Diabetic Fatty Rats

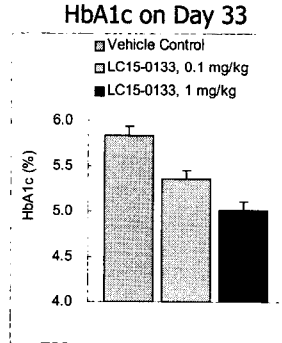
Blood Glucose Profile



Plasma Insulin Profile



HbA1c on Day 33



Animal: male Zucker Diabetic Fatty Rats, 6 weeks old on Day 1, n=8
Dosing: once daily, oral gavage
Vehicle: 100 mM glycine HCl buffer

LC15-0133 delayed the progression of diabetic symptoms in the male ZDF Rats

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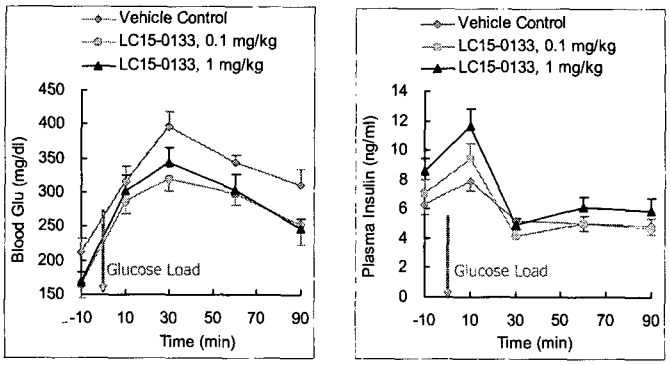
Chronic Effects in Zucker Diabetic Fatty Rats

OGTT (on Day 28, 10 weeks old): 46hr after the last dosing



Treatment: qd X 28, oral gavage

LC15-0133 improved glucose tolerance in the male ZDF Rats

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In vivo Efficacy - Summary

	LC15-0133
50% inhibition of DPP IV after 12 hr (SD rats)	0.03 mg/kg
MED for lowering glucose excursion (C57BL/6 mice)	0.01 mg/kg
MED for glucose induced GLP-1 increase (C57BL/6 mice)	0.1 mg/kg
MED for lowering glucose excursion (DIO mice)	0.025 mg/kg
MED for HbA1c reduction (ZDF rats): qd, 4 weeks	0.1 mg/kg

- **LC15-0133 shows excellent *in vivo* efficacy in various animal models, which seems due to a long duration of action**
- **Also shows excellent *in vivo* potency in an OGTT & HbA1C reduction in a long term administration studies**

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Non-Clinical Safety

Genotoxicity Tests

Test	Test System & Condition	Results
Bacterial Reverse Mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and *E. coli* WP2 uvrA 33~5000 ug/plate both in the absence and presence of 5~10% S9 mix	Negative at all dose levels in all test strains
Chromosome Aberration	Cultured Chinese Hamster Lung Cells 1200~5000 ug/ml in the absence of S9 mix 2500~5000 ug/ml in the presence of S9 mix	Positive Above 2500 μg/ml dose levels in the absence of S9 mix
Micronucleus	ICR mice (male & female) 500, 1000, 2000 mg/kg oral gavage for 3 days	Negative at all dose levels

Non-Clinical Safety

In Vivo Toxicity Studies

Test	Species/Dose	Results
7-Day Repeated Dose Range Finding Studies	SD rats 25, 50 and 100mg/kg, oral gavage	Well tolerated at 25 mg/kg (> 200 fold of efficacy dose)
	Beagle dogs 2, 5, 10 and 20 mg/kg, oral gavage	MTD = 2 mg/kg
28-Day Repeated Dose Toxicity with 2-Week Recovery	SD rats 6, 12.5, 25 and 50 mg/kg, oral gavage	NOEL = 12.5 mg/kg
	Beagle dogs 0.5, 1 and 2 mg/kg, oral capsule	NOAEL = 2 mg/kg

Safety Pharmacology Studies

- **Negative in HERG assay**
- **No pharmacological effect up to 50 mg/kg in CNS and respiratory system**

LG 생명과학의 DPP IV 억제제 개발 현황

백업인 LC15-0444의 임상2상 시험 진행 중 (07년 11월 IND 승인)

Key Features of LC15-0444

- Potent and selective
- Superior pharmacodynamic profiles in mice, rats, dogs, and monkeys, compared to sitagliptin
- Long plasma half-life: Potential for once daily dosing
- Good safety profile from Phase I clinical study and 3-month repeated toxicity studies (rat, dog)

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