Overview of Chugai Diabetes

CHUGAI PHARMACEUTICAL CO.,LTD.
Department Manager
Project Management Dept.
Hisanori Takanashi

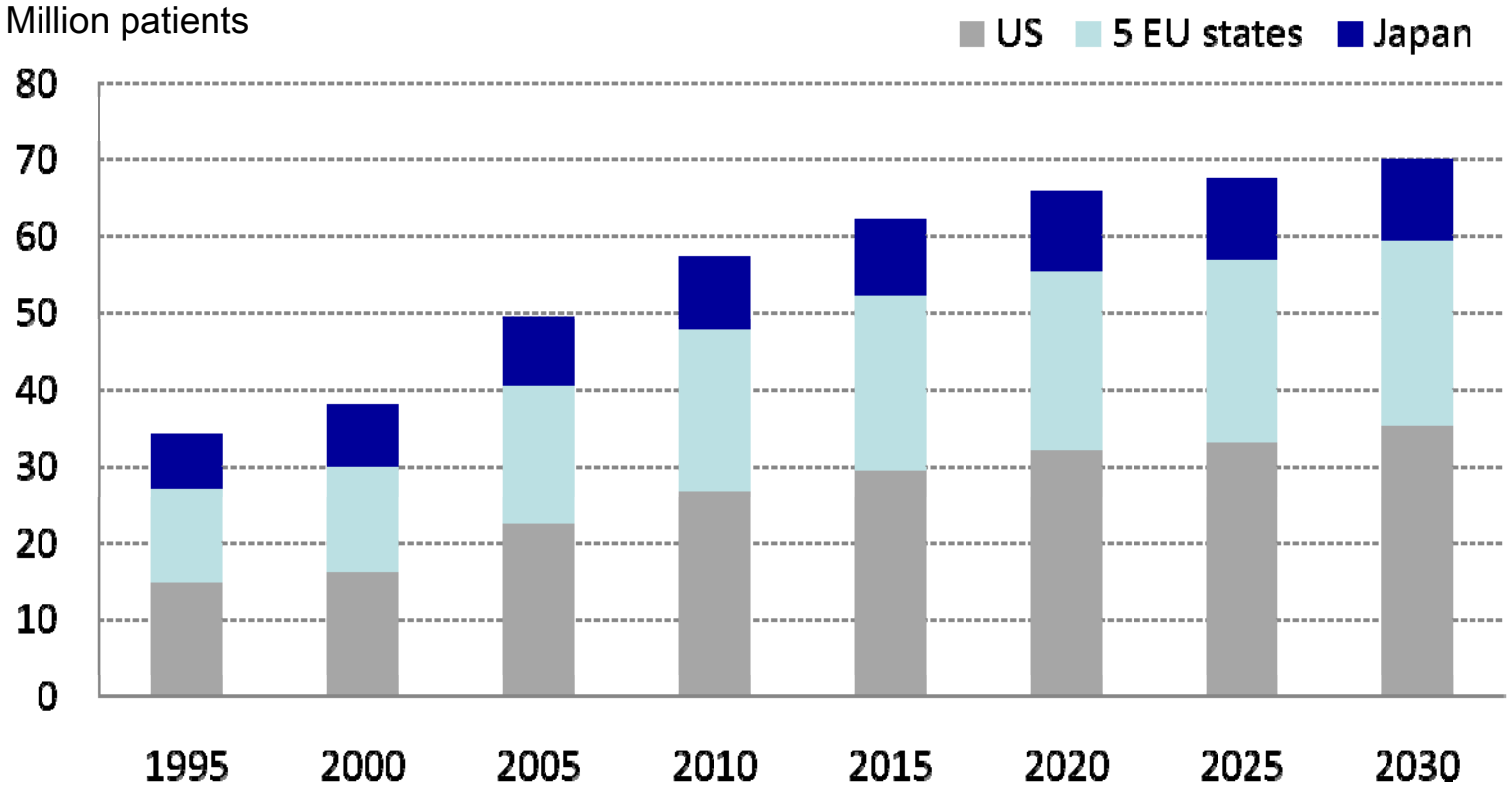
December 7, 2009

Forward-Looking Statements

This presentation may include forward-looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. (the “Company”). These statements reflect the Company’s current analysis of existing information and trends. Actual results may differ from expectations based on risks and uncertainties that may affect the Company’s businesses.

Contents

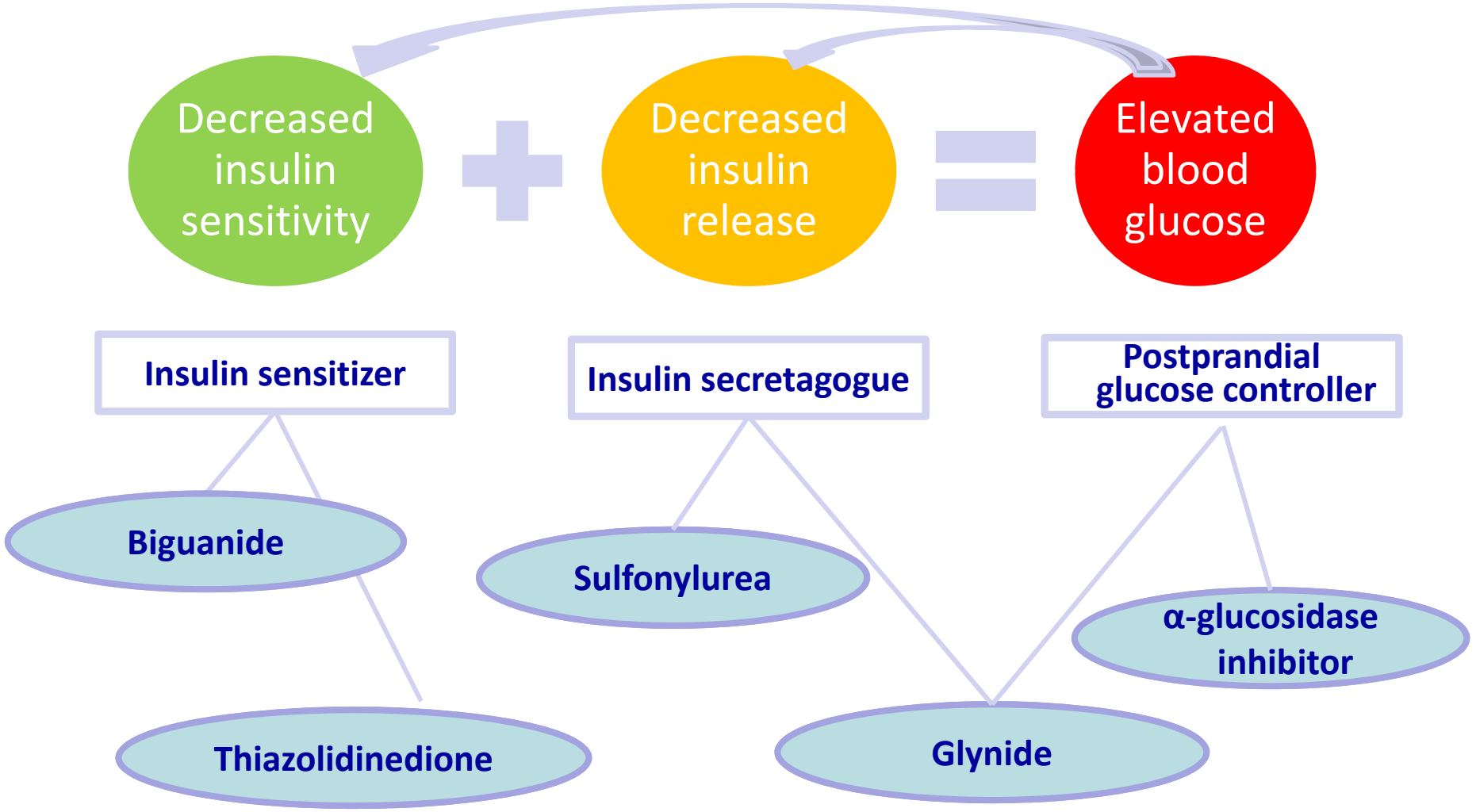
Diabetes Population



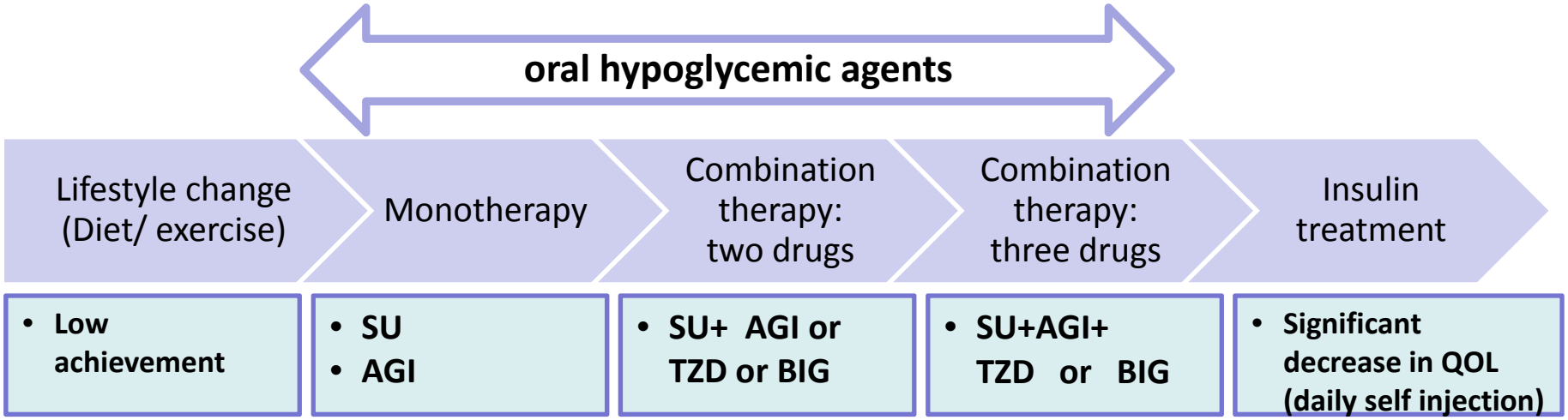
5 EU states: UK, France, Germany, Italy and Spain

Epi Database (MattsonJack / Synix Co.)

Oral Agents for Type 2 Diabetes in Japan



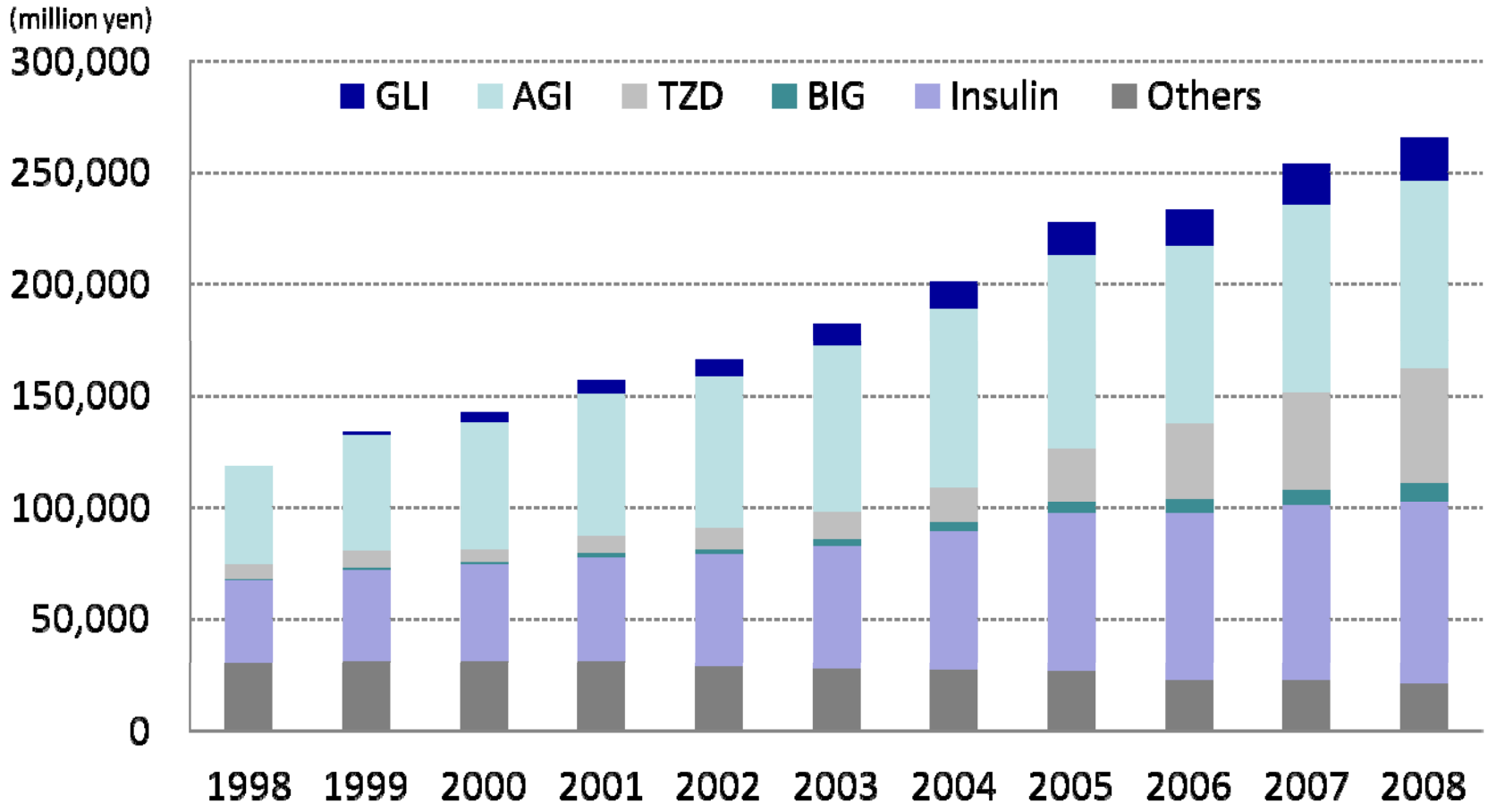
Current Treatment Algorithm in Japan



Treatment guidelines in Japan:

- Oral treatment should start if a patient cannot achieve sufficient glucose control after lifestyle change (diet and exercise).
- In choosing drugs, consider clinical factors like disease status, complications and drug mechanism.
- Drug administration should start at low dose. Increase dosage depending on patients' clinical status. Before starting SU, patients should be well informed of what should be done in case of hypoglycemia.
- Other treatment approach including combination therapy should be considered if a patient cannot achieve target glucose level 3 months after treatment.

Diabetes Market in Japan NHI reimbursement price basos

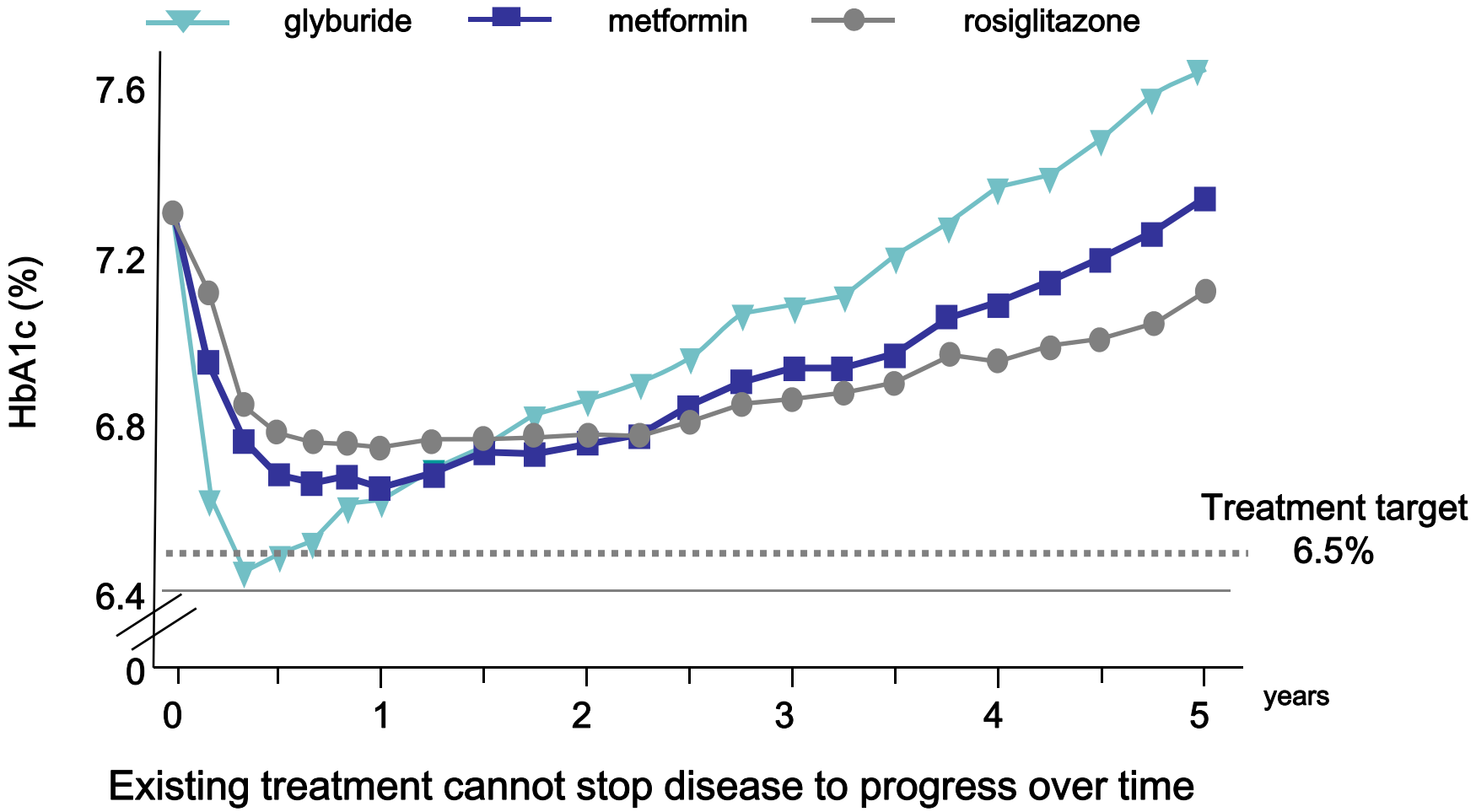


Source：JPM 1998 - 2008 Dec. MAT, Reprinted with permission
The scope of the market is defined by Chugai.

Contents

Effect Duration (ADOPT)

Previously-untreated patients



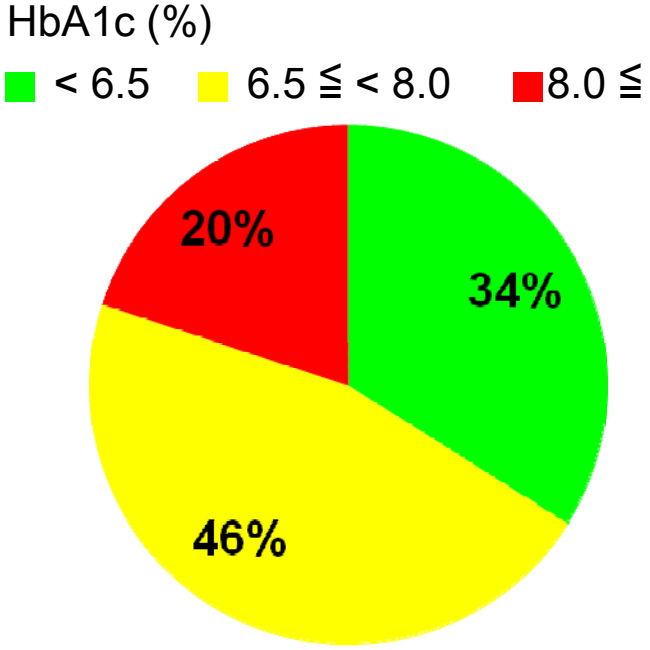
Existing treatment cannot stop disease to progress over time

Kahn SE et al. N Engl J Med 2006;355:2427-43.

Glucose Control and HbA1c

Glucose control

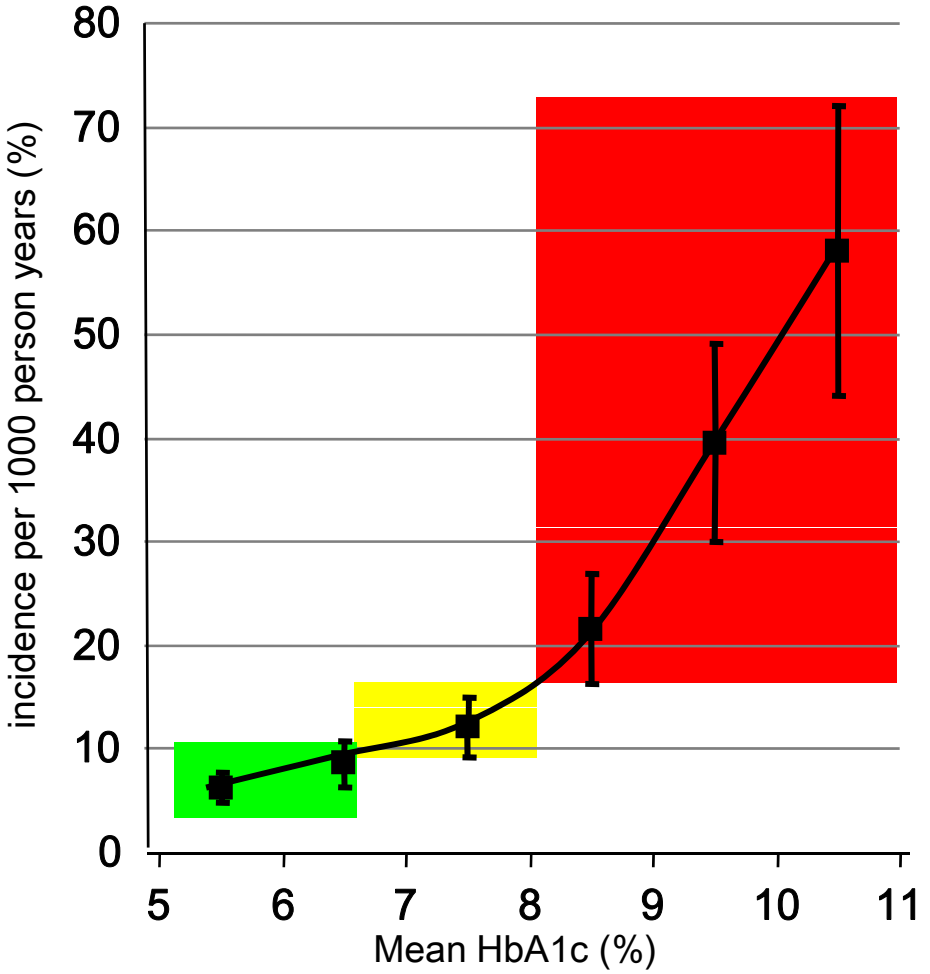
Only 34% of patients with diabetes achieves desirable status



# of patients
type 1: 793, type 2: 16,141

Kobayashi M. et al. Diab Res Clin Pract 2006;73:198-204.

HbA1c and microvascular complications



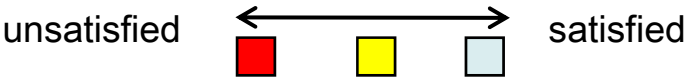
Stratton IM. et al. BMJ 2000;321:405-412.

Profiles of Existing Treatments

Treatment satisfaction

	Insulin sensitizer		Insulin secretagogue		Others
	SU	GLI	BIG	TZD	AGI
HbA1c reduction	+++	+	++	+++	+
Duration of glucose control	-	-	±	±	±
Effect on weight	↑	↑	~	↑	~
Hypoglycemia risks	++	+	-	-	-
Edema	-	-	-	++	-
Gastrointestinal disorder	-	-	+	-	+
Contraindication	-	-	+	+	-
Ease of administration	QD	TID	TID	QD	TID

QD: Once daily, TID: Three times daily



Contents

Entry into Diabetes Area

- High unmet medial needs
  - Increasing number of patients
  - Challenges with existing treatments (glucose control sustainability)

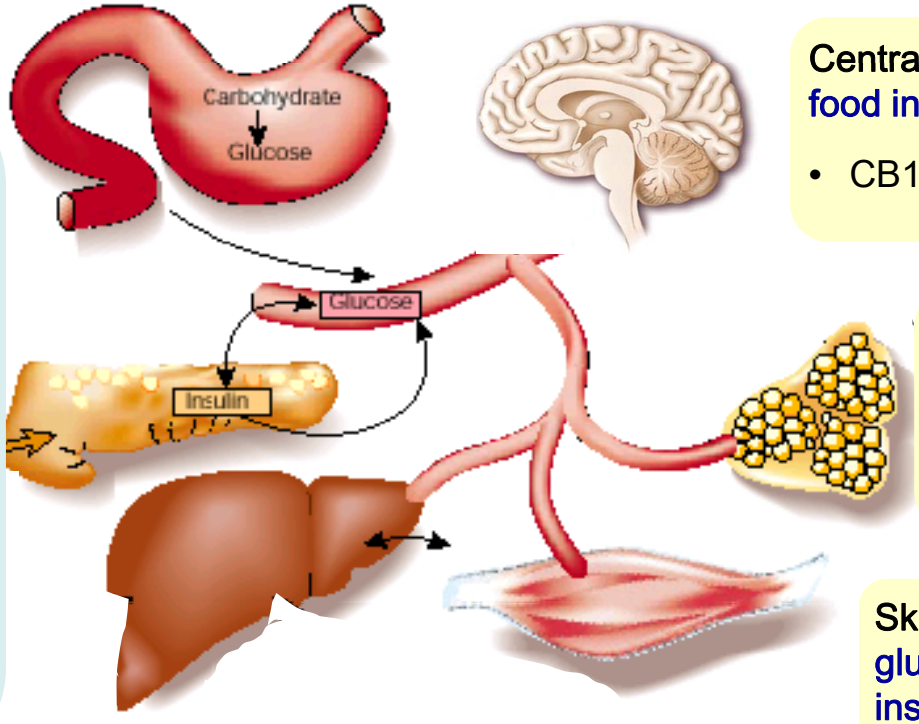
- Enhanced R&D capabilities through the alliance with Roche
  - Sharing of research infrastructure
  - Global development through group network
  - Synergies with Roche Diagnostics

- Strategies
  - Epogin and other renal franchise - increase in chronic renal failure in patients with underlying diabetes
  - Presence in GP market
  - Euglucon business

Target Organs for New Treatments

Pancreas :
glucose-dependent insulin secretion↑
glucose-dependent glucagon secretion↓
enhance β-cell regeneration

- GLP-1 agonist
- DPP-4 inhibitor
- Other secretagogue
- Glucagon receptor antagonist



Central nervous system:
food intake↓

- CB1 antagonist

Fat :
glucose uptake↑
insulin sensitivity↑

- 11β-HSD-I

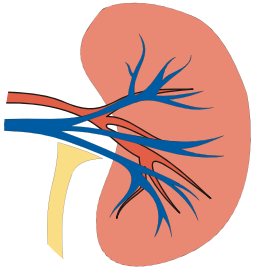
Skeletal muscles:
glucose uptake↑
insulin sensitivity↑

Liver :
gluconeogenesis ↓
glucose uptake↑

- Glucokinase activator

Kidney :
glucose uptake ↓

- SGLT2 inhibitor



Profiles of New Treatments

Treatment satisfaction

	Insulin sensitizer				Insulin secretagogue		Others	
	SU	GLI	DPP-4	GLP-1	BIG	TZD	AGI	SGLT2
HbA1c reduction	+++	+	++	++++	++	+++	+	+++?
Duration of glucose control	-	-	?	?	±	±	±	?
Effect on weight	↑	↑	~	↓	~	↑	~	↓
Hypoglycemia risks	++	+	-	-	-	-	-	-
Edema	-	-	-	-	-	++	-	-
Gastrointestinal disorder	-	-	-	++	+	-	+	-
Contraindication	-	-	-	-	+	+	-	±
Ease of administration	QD	TID	QD	Injection	TID	QD	TID	QD

QD: Once daily, TID: Three times daily

unsatisfied ← → satisfied

Chugai's Approach

Challenges with existing therapies

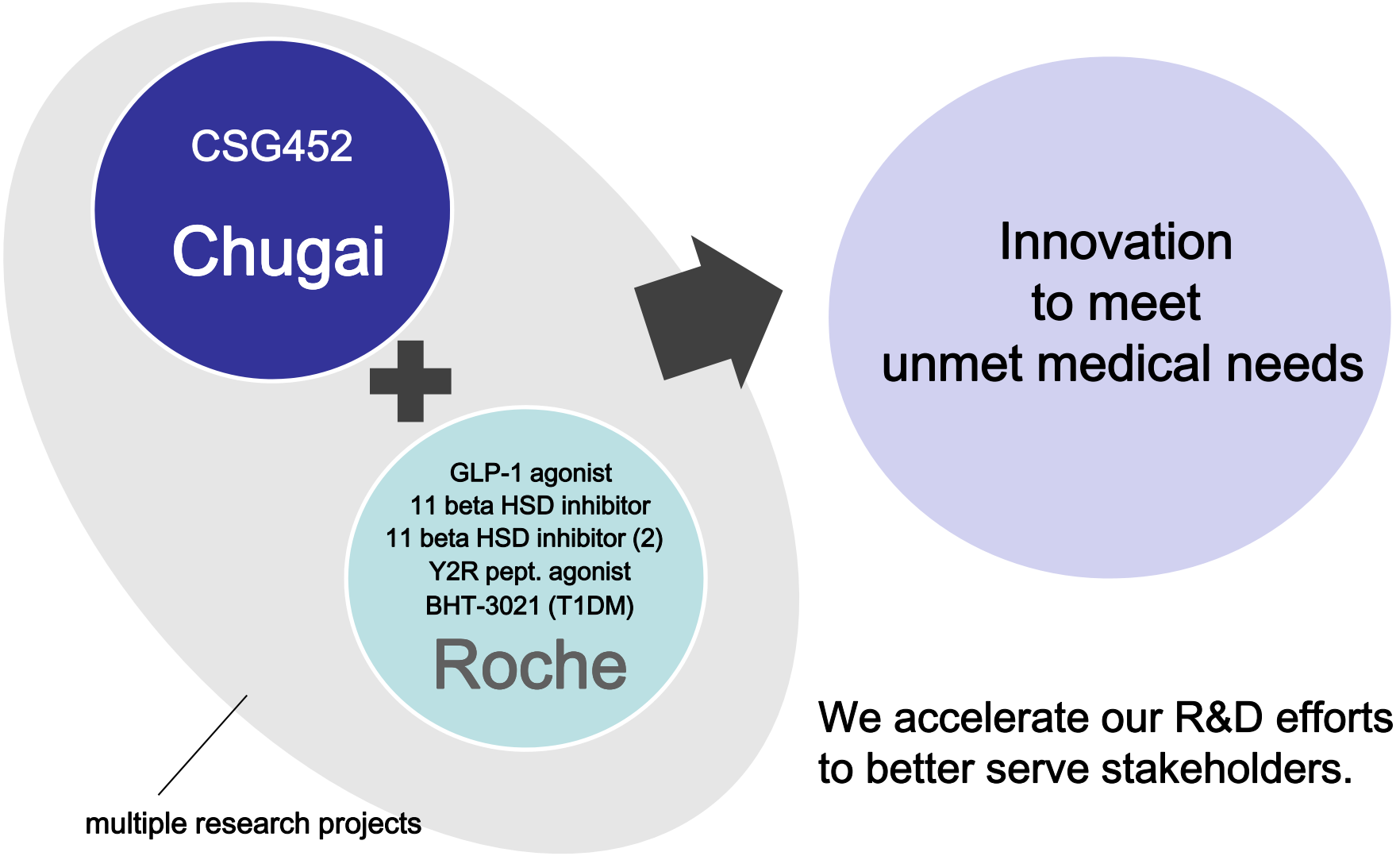
- Unsustainable efficacy
- Dose limiting side effects (hypoglycemia, weight gain, edema, GI disorder)

Expectations for new therapies

- Sustained control of blood glucose
- No hypoglycemic risks
- Weight neutral/weight loss
- Disease modifying effect (β-cell protection)

Aim at first-in-class and best-in-class with focus on: insulin secretagogues and disease-modifying candidates

To provide new treatment option



We accelerate our R&D efforts
to better serve stakeholders.

Overview of taspoglutide

CHUGAI PHARMACEUTICAL CO.,LTD.
Project Management Dept.
Takaki Koga

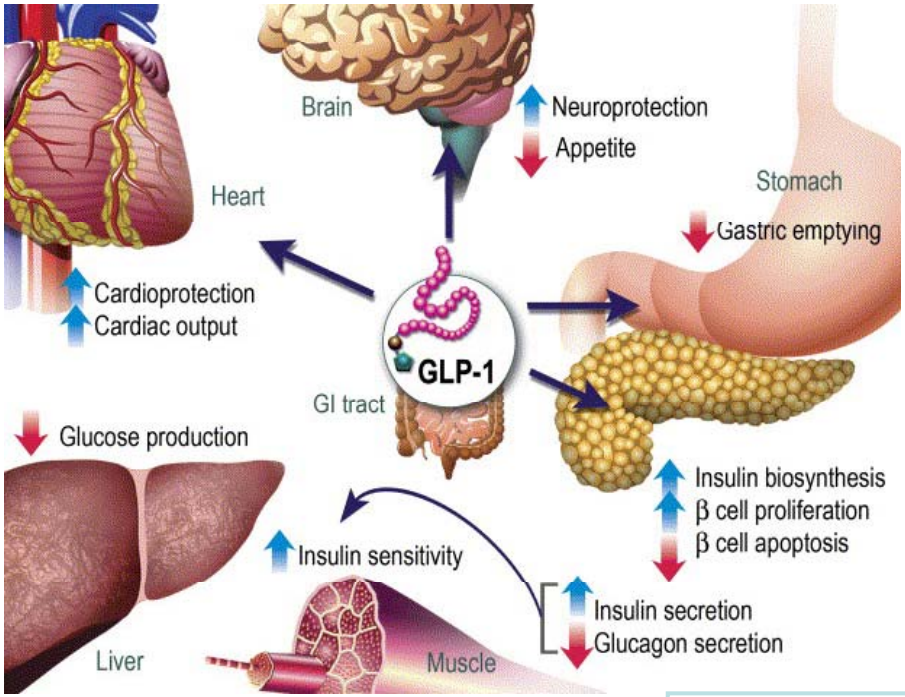
December 7, 2009

Contents

1. Biological actions of GLP-1 and its agonists under clinical developments
2. Profile of taspoglutide and its development status

Biological Actions of GLP-1 and its Application to Therapeutic Agents

Blood glucose lowering effect through glucose dependent stimulation of insulin secretion (incretin effect)



- Glucose conc. dependent
  - Insulin secretion stimulation
  - Glucagon secretion inhibition
- Gastric emptying delay
- Appetite suppression
- Body weight reduction
- Beta cell protection/regeneration

Diadvantage: Short half life

T1/2 = 2 min.

Long acting analogues
- Exenatide
- Liraglutide
- Taspoglutide

Degradation Enzyme inhibitors
- Sitagliptin
- Vildagliptin
- Alogliptin

Drucker, Cell Metabolism 2006;3:153-165

GLP-1 Agonists vs. DPP-4 Inhibitors

GLP-1: stronger blood glucose control and weight loss

	GLP-1 agonists	DPP-4 inhibitors
MOA	Pharmacological GLP-1 receptor potentiation	Enhancement of intrinsic incretin actions
Mode of administration	Injection	Oral
Glucose lowering	HbA1c reduction>1%	HbA1c reduction <1%
Body weight	Reduction	Neutral
Adverse events	Nausea, Vomiting	Highly tolerable
Hypoglycemic events	Noted when administered with SU	None

GLP-1 Agonists under Development in Japan

	Company	description	Administration	Status
Exenatide	Amylin/Lilly	Exendin-4 / solution	BID	NDA
Liraglutide	Novo Nordisk	GLP-1 analogue	QD	NDA
Lixenatide	Sanofi-Aventis	GLP-1 and Exendin-4 analogue	QD	P3
Exenatide LAR	Amylin / Lilly/ Alkermes	Exendin-4 / polymer-based microspheres	QW	P3
Taspoglutide /ITM-077	Roche/Ipsen/Chugai/Teijin	GLP-1 analogue / low pH solution containing Zn	QW	P2
Albigultide	GSK	GLP-1-albumin fusion	QW	P1/2
LY2189265	Lilly	Fc-fusion protein GLP-1 analog	QW	P2

QD: Once daily, BID: Twice daily, QW: Once weekly

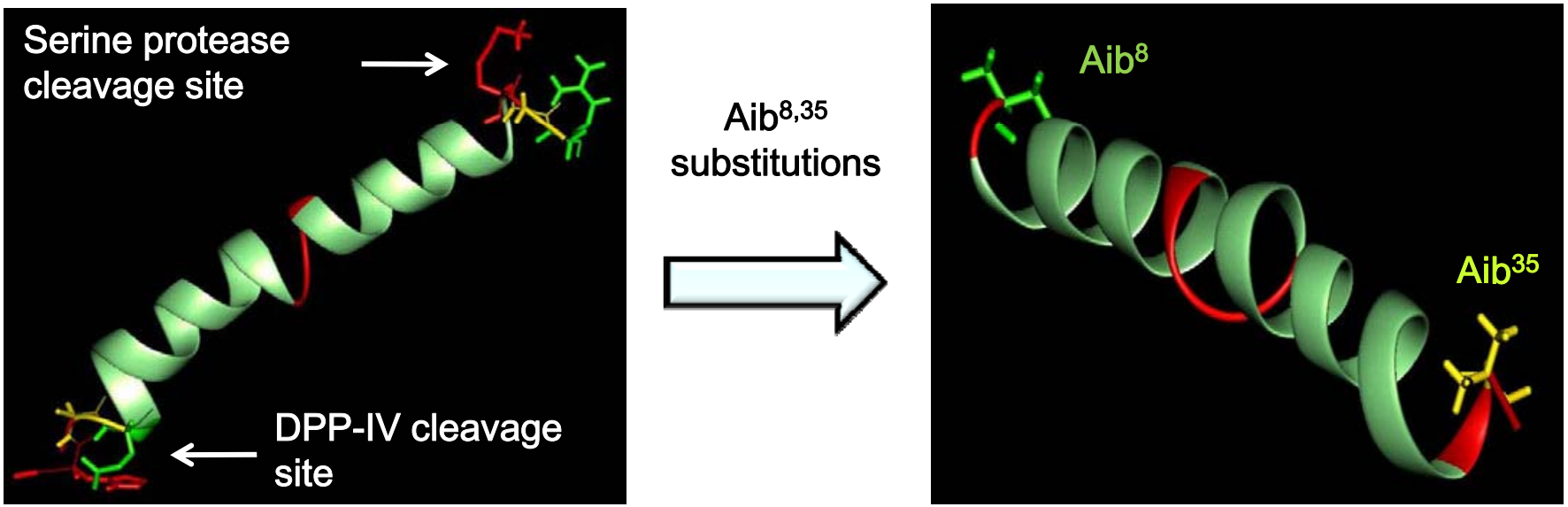
Contents

1. Biological actions of GLP-1 and its agonists under clinical developments
2. The profile of Taspoglutide and development status

Converting Native GLP-1 into Taspoglutide

Native GLP-1

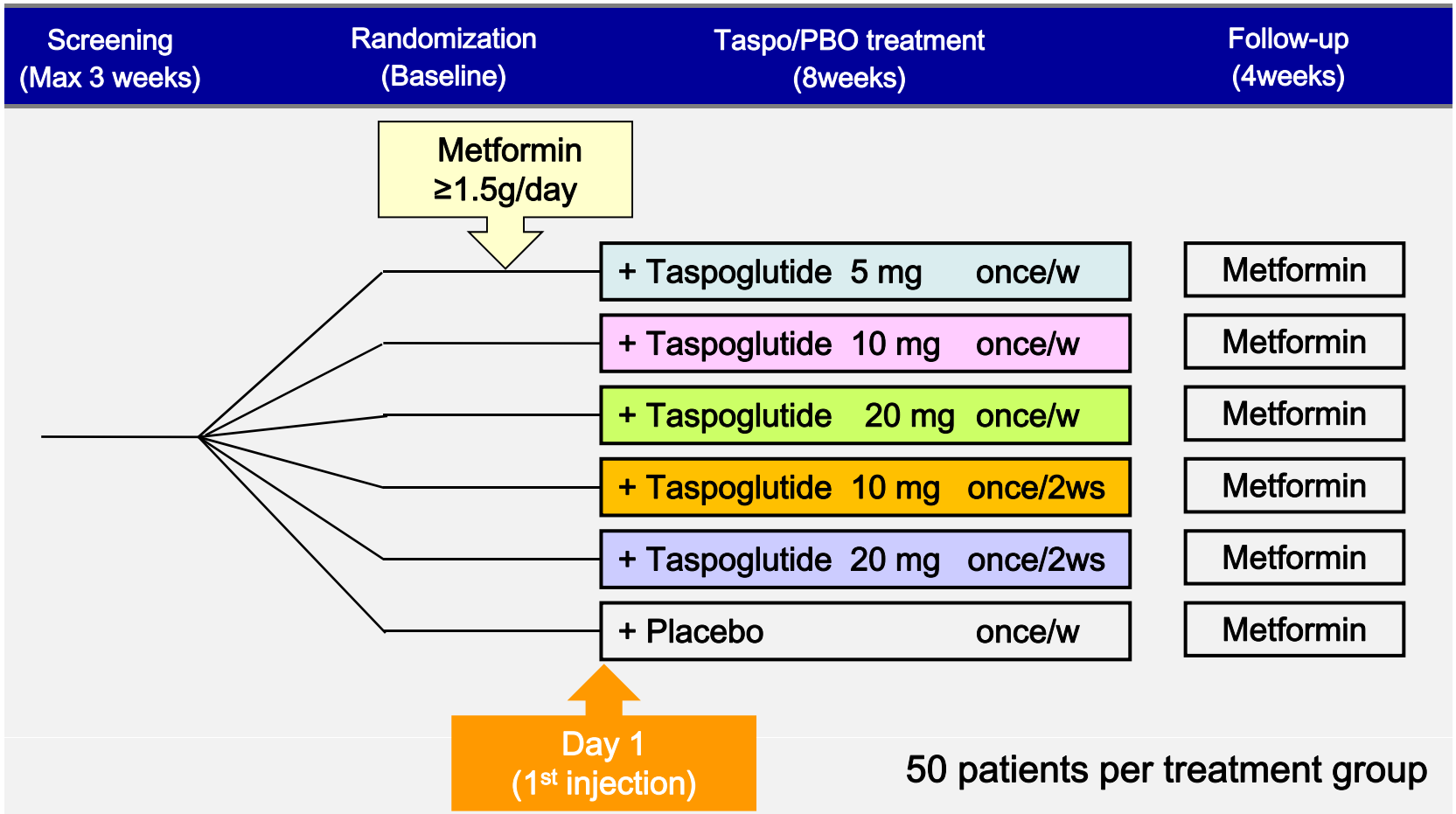
Taspoglutide



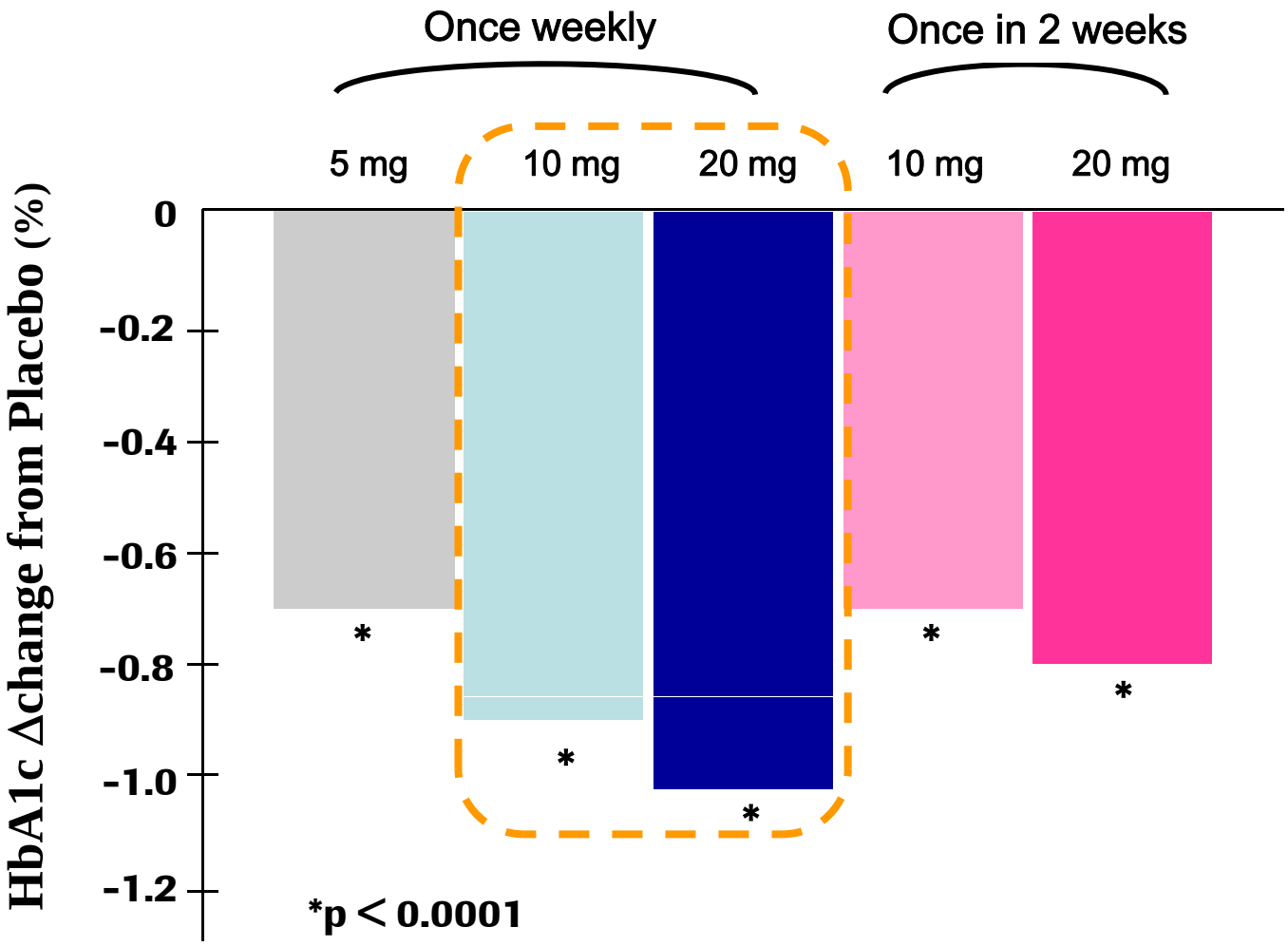
- The active form of native GLP-1 is rapidly degraded by peptidases
- Aminioisobutylic acid (Aib) substitutions block enzymatic degradations
- Agonist activity comparable with native form
- Once weekly dosing supported by zinc-based formulation

Overseas Phase 2 study

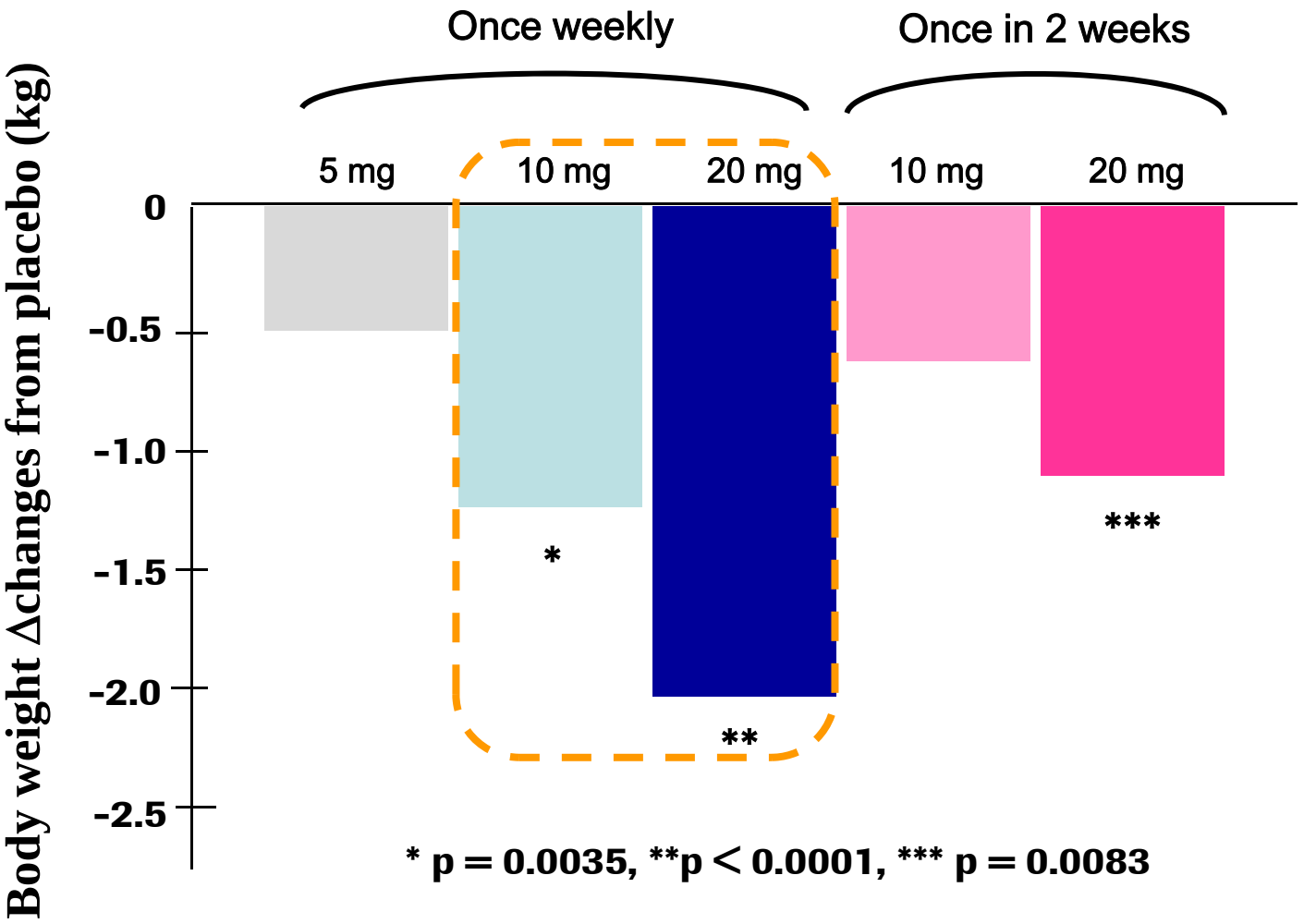
- once weekly or once in two weeks injections, metformin combination -



Changes in HbA1c: Significant Reductions in Only Eight Weeks



Changes in Body Weight: Significant Loss in Only Eight Weeks



Adverse Events

	Once weekly				Once in two weeks	
	Placebo n=49	5mg n=50	10mg n=49	20mg n=50	10mg n=50	20mg n=49
Nausea, n (%)	3 (6)	11 (22)	12 (24)	26 (52)	16 (32)	20 (41)
Diarrhea, n (%)	4 (8)	4 (8)	5 (10)	5 (10)	8 (16)	9 (18)
Vomiting, n (%)	2 (4)	2 (4)	2 (4)	11 (22)	6 (12)	12 (24)
Headache, n (%)	3 (6)	1 (2)	3 (6)	6 (12)	7 (14)	6 (12)
Decreased appetite, n (%)	-	-	5 (10)	3 (6)	4 (8)	3 (6)
Dyspepsia, n (%)	-	-	4 (8)	6 (12)	3 (6)	2 (4)
Abdominal distension, n (%)	-	-	2 (4)	2 (4)	3 (6)	6 (12)

Gastrointestinal effects most frequent → titrated administration adopted in Phase III studies for reduction

Ongoing Phase 3 Studies by Roche

Study name	Background medications	Comparators	N	Results
T-emerge 1	Diet & exercise	Placebo	330	Taspoglutide demonstrated superior HbA1c reduction versus placebo.
T-emerge 2	Metformin, TZD, Metformin + TZD	Exenatide	990	Taspoglutide demonstrated superior HbA1c reduction versus exenatide following 24 weeks of treatment.
T-emerge 3	Pioglitazone + metformin	Placebo	330	
T-emerge 4	Metformin	Sitagliptin	630	Taspoglutide demonstrated superior HbA1c reduction versus sitagliptin.
T-emerge 5	Metformin + SU	Insulin glargin	990	
T-emerge 6	SU ± metformin	Pioglitazone	650	
T-emerge 7	Metformin (high BMI)	Placebo	260	
T-emerge 8	History of cardiovascular event	Placebo	2000	

Taspoglutide: Advantage over Competitors

	Taspoglutide	Exenatide	Liraglutide	Exenatide LAR
Origin	Human	Lizard	Human	Lizard
Administration	Once weekly	Twice daily	Once daily	Once weekly
Efficacy (HbA1c)	> exenatide (T-emerge 2)		> exenatide (LEAD6)	> exenatide (DURATION1)
Device	Autoinjector (TBD)	Pen	Pen	Vial, prepared at each use

Development in Japan

Development code： ITM-077/RG1583
Originator： Ipsen/Roche
Partner： Co-development with Teijin Pharma
Chemical Structure： Human GLP-1 analogue
Formulation： Injection (sustained-release with zinc-based formulation)

< Ongoing study in Japan >

Study name	Phase 2 clinical study of ITM-077/RG1583 in type 2 diabetes mellitus patients.
Conducters	Teijn Pharma / Chugai Pharmaceutical
Summary	To investigate the efficacy, safety and dose-response of ITM-077/RG1583 after 12 weeks treatment in comparison with placebo in type 2 diabetes mellitus patients.
Administration	Once weekly, sc at abdomen
Design	Multi-center, double-blind, randomized, placebo-controlled, parallel intergroup study
Primary endpoint	Efficacy (HbA1c), safety

Overview of CSG452

CHUGAI PHARMACEUTICAL CO.,LTD.
Project Management Dept.
Global Project Leader
Sachiya Ikeda

December 7, 2009

Contents

1. Profile of CSG452
2. Profile of SGLT2 inhibitor and its development status
3. Development status of CSG452

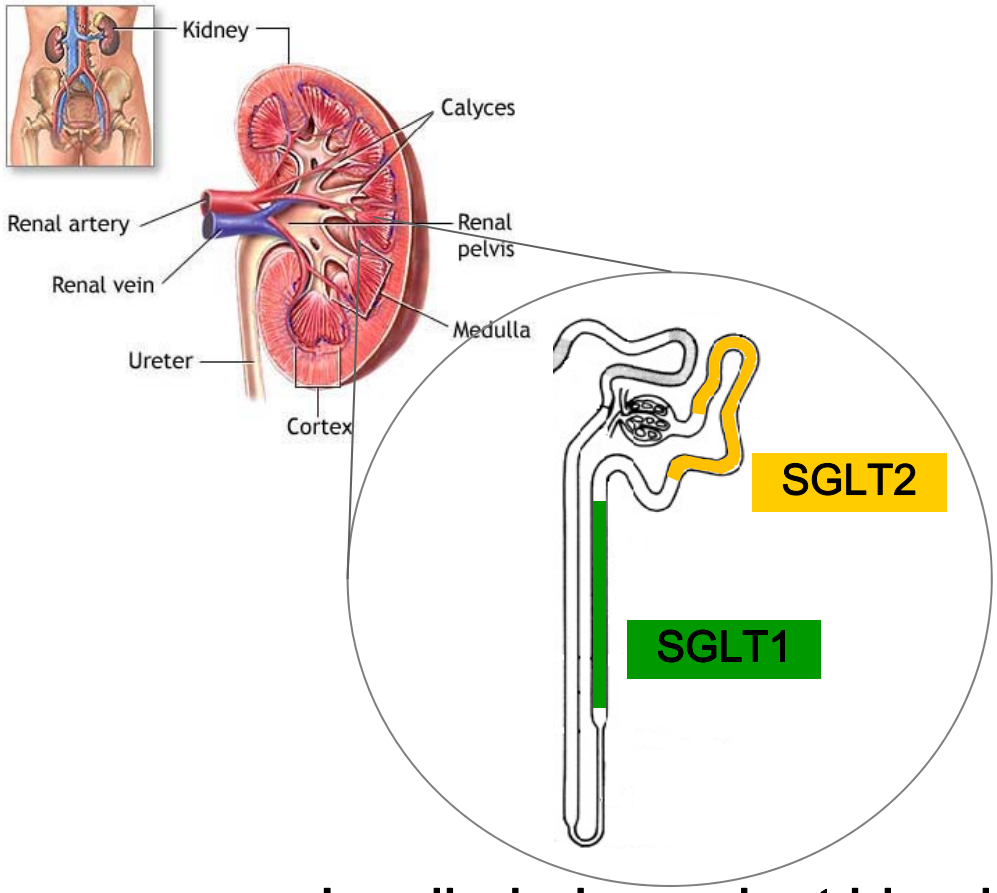
CSG452/ RG7201

The compound is;

- Selective SGLT2 inhibitor(*C*-glycoside) created at Fuji-Gotemba Laboratory, Chugai
- Co-development with Roche since 2007
- Ongoing global phase 2 (dose finding) study including participation from Japan
- FDD scheduled in 2010

Mode of Action of CSG452

- Blood glucose control through direct glucose excretion



- *Sodium glucose co-transporter (SGLT)* causes renal tubular reabsorption of blood glucose after glomerular filtration
- CSG452 prevents reabsorption of glucose by selectively inhibiting SGLT2, which carries larger transportation capacities between the two SGLTs in kidney. The blood glucose level is decreased as a result of glucose excretion in urine.

Insulin-independent blood glucose control is achieved

Contents

Profile of SGLT2 inhibitor

Indication

- Type 2 diabetes (possible Type 1 diabetes and pre-diabetes)

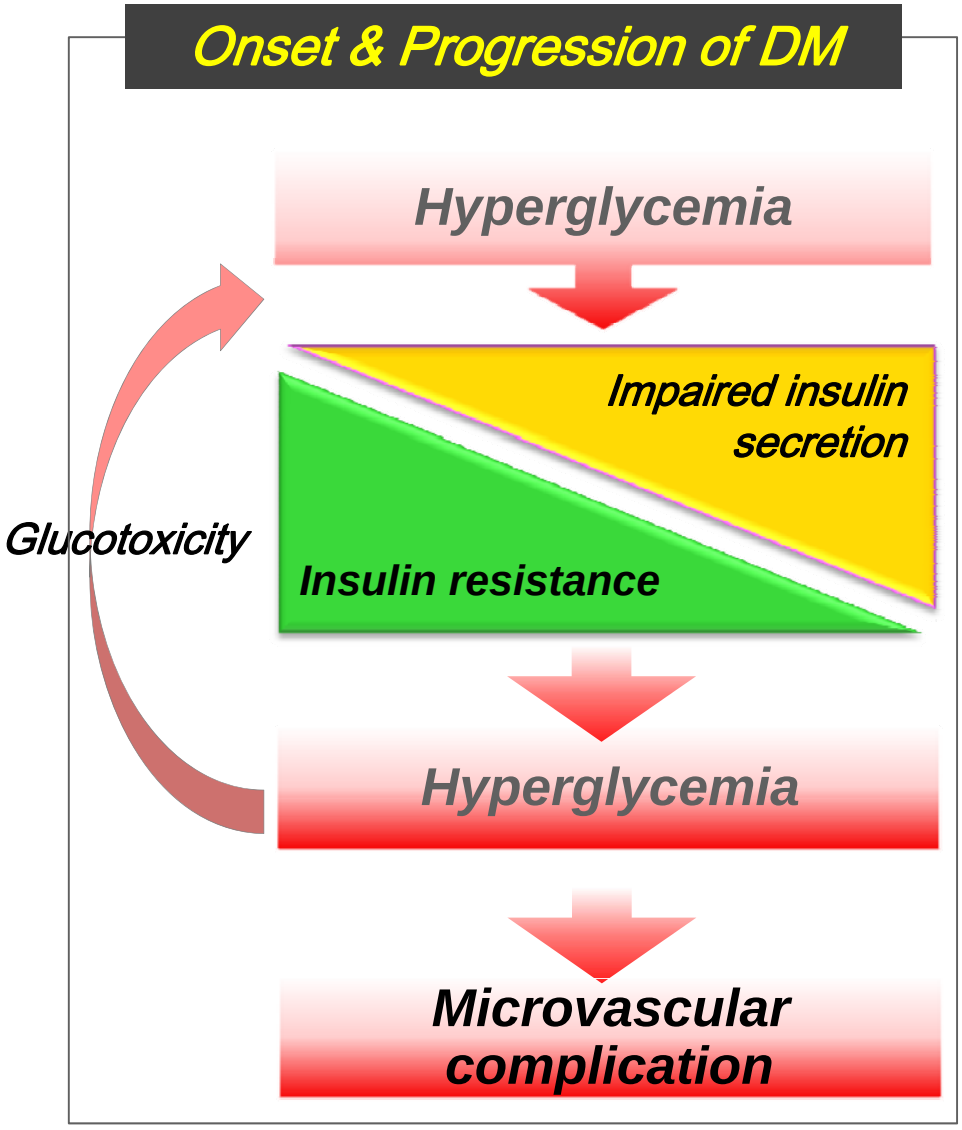
Differentiation from existing drugs

- Sustained blood glucose control irrespective of patient background
- Body weight /Blood pressure reduction
- Anti-diabetic effects by cancellation of glucotoxicity
- Low hypoglycemic risk
- High safety and tolerability (no GI disturbance, no edema)
- Combined with all anti-diabetics theoretically

Safety issues to be evaluated in long term studies

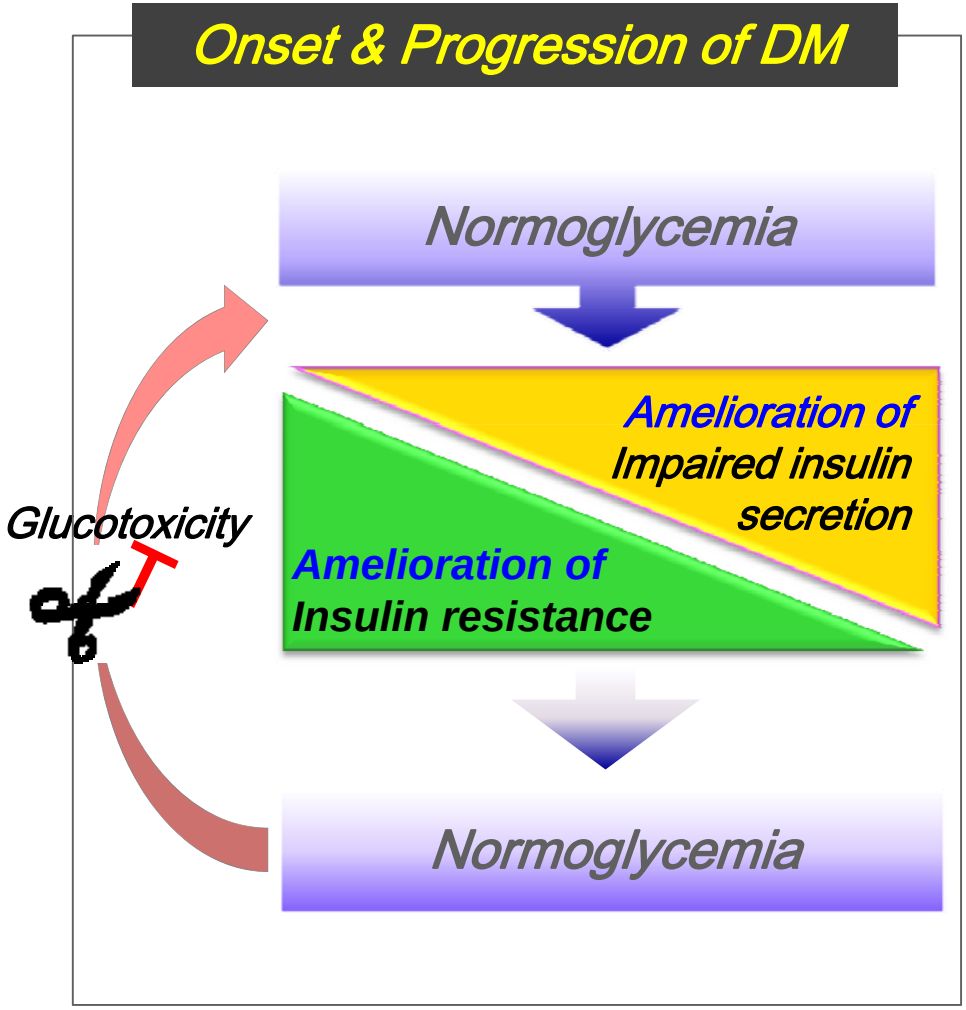
- Incidence of urinary tract infection and/or genital infection
- Water imbalance (polyuria, nocturia, dehydration, hypovolemia, increased haematocrit)
- Renal toxicity

SGLT2 inhibitor opens new insight into the diabetes pathophysiology “glucotoxicity”



- Sustained hyperglycemia impairs insulin secretion and inhibits insulin signaling (insulin resistance). This leads further hyperglycemia and it worsens impaired insulin secretion and insulin resistance then finally diabetes is developed
- This vicious cycle is called *GLUCOTOXICITY* and is thought to play a major role for onset and progression of diabetes mellitus

SGLT2 inhibitor opens new insight into the diabetes pathophysiology “glucotoxicity”



- Sustained hyperglycemia impairs insulin secretion and inhibits insulin signaling (insulin resistance). This leads further hyperglycemia and it worsens impaired insulin secretion and insulin resistance then finally diabetes is developed
- This vicious cycle is called *GLUCOTOXICITY* and is thought to play a major role for onset and progression of diabetes mellitus

European Journal of Internal Medicine 20 (2009) S329 – S339

Competitive landscape of selective SGLT2 inhibitor (as of Nov/2009)

Drug	Company	Dev. stage	
		Overseas	Domestic
Dapagliflozin	BMS/ AZ	P3	P2
Canagliflozin (TA-7284)	J&J/ Mitsubishi-Tanabe	P3	P1
CSG452 (R7201)	Chugai/ Roche	P2	P2
BI 10773	Boehringer Ingelheim	P2	P2
ASP-1941	Astellas	P2	P3
LX4211	Lexicon	P2	NA
ISIS 388626	Isis	P1	NA

Contents

Ongoing Clinical Trial

< P2 Multinational Study >

Title of the study	Investigate Glycemic Parameters of Efficacy, Safety/ Tolerability and Pharmacokinetics of Five Dose Levels of R7201/CSG452 in Patients With Type 2 Diabetes Mellitus
Sponsor	Chugai Pharmaceutical
Summary	12-week Study will evaluate the efficacy, safety and pharmacokinetics of 5 doses of R7201 compared to placebo in patients with type 2 diabetes mellitus.
Dose	Once daily, Oral
Study design	Treatment, Randomized, Double Blind (Subject, Investigator), Parallel Assignment, Safety/Efficacy Study 6 arm study (2.5mg, 5mg, 10mg, 20mg, 40mg, Placebo)
Inclusion Criteria	Either treated with diet, exercise and stable metformin, or with diet and exercise alone.
Primary Outcome	Absolute change in HbA1c

Contacts:

Corporate Communications Group

Tel: +81 (0)3-3273-0881 Fax: +81 (0)3-3281-6607
e-mail: pr@chugai-pharm.co.jp

Masayuki Yamada, Shinichi Hirose, Hiroshi Araki

Investor Relations Group

Tel: +81 (0)3-3273-0554 Fax: +81 (0)3-3281-6607
e-mail: ir@chugai-pharm.co.jp

Mac Uchida, Kae Maeda, Tomoko Shimizu, Yusuke Tokita