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Leveraging Nonclinical Safety Evaluation Findings to Expedite Next-Generation Glucagon-like Peptide-1 Receptor Agonists (GLP-1RAs) Development for Metabolic Disorders and Beyond

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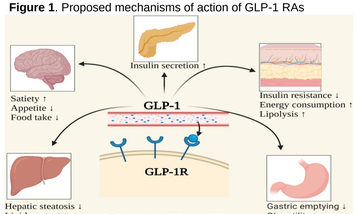
BACKGROUND

- Glucagon-like peptide-1 (GLP-1) / glucagon-like peptide-1 receptor (GLP-1R) system is one of the key incretin pathways that play an essential role in regulating hypoglycemic effects, energy balance, feeding behavior, and reducing weight.[1] Due to the short half-life (~2 min) and activity of natural GLP-1, global drug developers (including Novo Nordisk and Lilly) have developed a series of GLP-1R agonists (GLP-1RAs or GLP-1 analogs) with various delivery and half-life extension strategies, which represent an important and attractive class of medication for the management of type-2 diabetes (T2D) and obesity.
- GLP-1R is expressed mainly in the pancreatic islet (β-cells), also widely distributed in neurons (enteric, central, peripheral nervous system), gastrointestinal tract, cardiovascular system, kidney, lung, liver, immune system, and other organs or cell types.[2] By acting on multiple target tissues involved in glucose homeostasis, GLP-1RAs enhance glucose-dependent insulin production, decrease glucagon secretion, increase glucose uptake and glycogen synthesis in peripheral tissues, delay gastric emptying, increase satiety, and inhibit energy intake.[3] The MOA of GLP-1RAs is shown in **Figure 1**.

Figure 1. Proposed mechanisms of action of GLP-1 RAs



- Since the first approval of GLP-1RA (exenatide; Byetta™) by the US FDA in 2005, drug therapy for T2D and obesity has made significant progress with 15 approved GLP-1RA drugs
- Given GLP-1RA's preferable profile, currently there are >143 of these compounds in development.
- While GLP-1RAs share similar MOA, the nonclinical safety profiles of individual agents differ, particularly between short- and long-acting agents. Several key differences exist in terms of molecular properties, dose regimen, and pharmacokinetics, which likely led to discordant toxicity profiles. **These challenges potentially increase the Sponsors' risk of engaging in early-stage drug development and impede the progress of novel therapies.**

OBJECTIVE

- In this study, we conducted a systemic and retrospective review of the US FDA regulatory documents (*Pharmacology & Toxicology Review*) of approved GLP-1RAs to compile a database based on their **chemical structure, administration route, dose, and frequency, PK, nonclinical and clinical adverse effects.**
- By utilizing this synthesized regulatory information and knowledge, we aimed to **1) identify the class or specific adversity of novel GLP-1RA candidate drugs under early development at Altasciences and 2) provide insights and expertise to facilitate the development of transformative GLP-1RA therapies.**

KEY RESULTS

- Although frequency or rates of toxicological effects differ between specific agents, noteworthy findings across these products include:
  1. Thyroid C-cell hyperplasia and neoplasia in 2-year rodent carcinogenicity studies.
  2. Chronic pancreatic injury/pancreatic neoplasia in islet beta cells and/or exocrine duct cells in various animal models;
  3. In contrast, the most common adverse effects in humans are gastrointestinal-related symptoms and injection site reactions. There is no direct evidence of thyroid carcinoma in humans with a lower density of GLP-1R on C-cells compared to rodent models. A schematic overview and comparisons of approved GLP-1RAs are summarized in **Table 1**.

CONCLUSION AND BENEFITS FOR EMERGING GLP-1RA DEVELOPMENT

With considerable heterogeneity and complexity across the class of GLP-1RAs, each candidate agent should be evaluated independently instead of assuming a class effect. As an increasing number of newer-generation GLP-1RA-based therapies are being developed for chronic metabolic, cardiovascular, and neurodegenerative disorders and similar drug delivery strategies are also applied for these novel peptides, **understanding the entire product landscape is important to maximize product success. This retrospective review provides insights and considerations that can help accelerate the development of next-generation therapeutic GLP-1RAs.**

Nonclinical Adverse and Clinical Safety Findings of US FDA-approved Glucagon-like Peptide-1 Receptor Agonists (2005-2023)

Table 1. Analysis and comparison of GLP-1RAs by product characteristics, half-life extension strategies, ADME, and adverse effects. [4]

Subclassification	Trade Name	Active Ingredient	Approval Year (company)	Indication	Class and MOA	Molecular Structure	Homology to Native GLP-1	Prolonged Exposure Strategy	ADME	Safety Pharmacology	General Toxicology	Genotox and Carcinogenicity	DART	Dose Regimen	ADME	Common Adverse Reactions (≥5% in clinical trials patients)
Exendin-4 analogs (DPP-4-resistant); *short-acting*	Byetta	exenatide (immediate-release)	2005 NDA021773 (Amylin/Eli Lilly)	T2D	Mono-agonist GLP-1R		53%	Sequential modification (enhances DPP-4 resistance)	PK (SQ) in mice, rats, rabbits, and NHPs: A: **Byetta** Tmax 0.25-0.5 hrs in mice/rats, 0.4-1.75 hrs in rabbits/NHPs vs. **Bydureon** dual-phasic release Tmax 3-4 days and 23-28 days in rats/NHPs (bioavailability or BA 65-75% in rats; 23% in NHPs); ADA in rats/NHPs (not neutralizing) D: plasma albumin-bound 82%; low amount cross placental barrier and in milk M: proteolytic degradation E: **Byetta** t½ 1.5-3.6 hrs in rats; excretion via urine (no parent compound) ***Similar PK profile of Bydureon and Bydureon BCise in rats and NHPs***	CNS, CVS, and respiratory functions in mice and NHPs: No adverse effects at the human exposure	Pivotal Tox (Byetta) in mice, rats and NHPs for 3, 6 and 9 mos: 1. Mice: ophthalmology findings, injection sites reaction, parotid salivary gland basophilia at all doses; testis and bone marrow effects (260X MRHD AUC human exposure or HE) 2. Rats: decreased FC/BW; adrenal gland (vacuolar change), pancreas lymphocyte infiltration, parotid salivary gland basophilic foci (129X HE) 3. NHPs: decreased FC/BW; microscopic findings in lung, brain, thyroid, adrenal gland, kidney, heart, skeletal muscle, pancreas, sciatic nerve, uterus, GI lesions and injection sites (65X-1860X HE); antigenic to NHP (not neutralizing) *Bridging studies (Bydureon) in rats 1 and 4 mos and NHPs 3 and 9 mos:* ***Rats/NHPs: reversible injection-site reactions in all groups receiving microspheres***	Carci in 2-year rats and mice: 1. Rats: significant increase in thyroid C-cell adenomas (F only) at 5-130X HE (**Byetta**); increased C-cell tumors (adenomas and carcinomas) at 2-27X HE (**Bydureon and Bydureon Bcise**) 2. Mice: no tumors up to 95X HE (**Byetta**); carcinogenicity not evaluated for **Bydureon and Bydureon Bcise** 3. Not mutagenic or clastogenic in a standard battery of genotoxicity tests	DART in mice, rats, and rabbits: 1. Mice: cleft palate, irregular fetal skeletal ossification, neonatal mortality (1X HE) 2. Rats: reduced fetal growth at all doses and irregular fetal skeletal ossification (with decreased maternal FC/BW) at 7-17X HE 3. Rabbits: irregular fetal skeletal ossification (4X HE)	Twice daily 5-10 µg (SQ)		GI-related: nausea, vomiting, diarrhea, dyspepsia, constipation; others: hypoglycemia, feeling jittery, dizziness, headache, asthenia
	BYDUREON	exenatide (extended-release)	2012 NDA022200 (AstraZeneca)					Sequential modification + sustained release microspheres (aqueous)						Once weekly 2 mg (SQ)	A: Tmax 2.1 hrs (Byetta immediate-release formulation) or 6-7 wks (Bydureon microspheres) D: volume of distribution (Vd) 28.3 L M: proteolytic cleavage (peptide) E: Clearance (CL) 9.1 L/h; half-life (t½) 2.4 hrs (immediate-release formulation); excretion via urine	GI-related: nausea, diarrhea, vomiting, constipation, dyspepsia; others: headache, injectionsite pruritus, injection-site nodule
	BYDUREON BCise	exenatide (extended-release + autoinjector)	2017 NDA209210 (AstraZeneca)					Sequential modification + microspheres (oily) + auto-device						Once weekly 2 mg (SQ)		GI-related: nausea; others: injection-site nodule
	Adlyxin	lixisenatide	2016 BLA208471 (Sanofi)	T2D	Mono-agonist GLP-1R		50%	Sequential modification	PK in mice, rats, dogs, and NHPs: Immunogenic response (ADA) in all species, data limited to A: accumulation due to ADA binding rats>mice>dogs>NHPs D: kidneys, lung, pancreas, adrenals, brain, across placenta in rats M: proteolytic degradation E: excretion via urine/feces ***SOLIQUA cross-reference Adlyxin and Lantus applications nonclinical PK/tox studies***	CNS, CVS, GI and respiratory function in mice, rats, and dogs: 1. Mice: decrease gastric emptying 2. Rats: hypoactivity, increase in MAP 3. Dogs: vomiting, diarrhea, reduced FC/BW 4. *in vitro*: inhibition of hERG currents	Pivotal Tox in mice, rats and dogs for 3, 6, and 12 mos: 1. Mice/Rats: no adverse findings 2. Dogs: GI effects with reductions in FC/BW; injection sites effects and microscopic changes in testes (hypospermatogenesis) and epididymis (dilation, degeneration, oligospermia or aspermia) at >140X HE (species-specific and relevance to humans unknown)	Carci in 2-year rats and mice: 1. Rats/Mice: significant increase in thyroid C-cell tumors (adenomas and/or carcinomas in M/F) at >15-56X HE (rats) and C-cell adenomas (M only) at >180X HE (mice) 2. Not mutagenic or clastogenic in a standard battery of genotoxicity tests	DART in rats and rabbits: 1. Rats: maternal toxicity (reduced FC/BW); fetal malformations/mortality 2. Rabbits: decreased maternal motor activity and FC/BW; delayed fetal growth, visceral and skeletal malformations, embryonic death ***Juvenile toxicity in rats/dogs: similar to adult rats/dogs with reduced FC/BW***	Once daily 10-20 µg (SQ)	A: Tmax 1-3.5 hrs D: Vd 100 L (plasma albumin-bound 55%) M: proteolytic cleavage E: CL 35 L/h; t½ 3 hrs; excretion via urine	GI-related: nausea, vomiting, diarrhea; others: headache, dizziness, hypoglycemia
	SOLIQUA	lixisenatide + insulin glargine (Lantus®)	2016 BLA208673 (Sanofi)		Combination: Mono-agonist GLP-1R + insulin glargine			Sequence modification + long-acting insulin						Once daily 15-60 units insulin glargine and 20 µg lixisenatide (SQ)	***Note: PK of lixisenatide not affected when administered as SOLIQUA 100/33***	GI-related: nausea, diarrhea, vomiting, decreased appetite, dyspepsia, constipation; others: immunogenicity-related urticaria (0.8%)
	Victoza	liraglutide	2010 NDA22341 (Novo Nordisk)	T2D	Mono-agonist GLP-1R		97%	Sequence modification + covalent attachment of fatty acid	PK in mice, rats, minipigs, and NHPs: A: Tmax 3-4 hrs in mice/rats, 12-24 hrs in NHPs/minipigs (BA 86% in NHPs) D: Vd 0.2 L/kg in NHPs; plasma albumin-bound 99% in all species (low levels cross BBB and placenta in rats/rabbits) M: proteolytic degradation E: t½ 7-54 hrs (mouse<rat<monkey); excretion via urine/feces/expired air/milk ***Saxenda and Xultophy cross-reference Victoza applications in nonclinical PK/tox studies***	CNS, CVS, respiratory, GI, and renal functions in rats, minipigs, and NHPs: 1. Rats: Increases in heart rate/MAP, decreases in body Temp, diuresis 2. Minipigs: delayed gastric empty 3. NHPs: no effect on QTc interval	Pivotal Tox in mice, rats, rabbits, and NHPs for 3, 6, and 12 months (well-tolerated): 1. Mice: no adverse findings 2. Rats/rabbits/NHPs: decreased FC/BW gain along with clinical signs of toxicity; irreversible injection site reactions (inflammation/fibrosis) in NHPs Additional local toxicity (Victoza and Saxenda) in pigs: mild injection site reactions (inflammation, hemorrhage, and/or fibrosis)	Carci in 2-year rats and mice: 1. Rats/Mice: significant increase in thyroid C-cell tumors (adenomas and/or carcinomas in M/F) at 0.5-8X HE (rats) and at 10-45X HE (mice); malignant fibrosarcomas in the dorsal skin and subcutis in male mice. 2. Not mutagenic or clastogenic in a standard battery of genotoxicity tests ***Human relevance of thyroid C-cell tumors in mice and rats is unknown and has not been determined by clinical or nonclinical mechanistic studies.***	DART in rats and rabbits: 1. Rats: teratogenic in rats; increase in early embryonic deaths (11X HE) with reduced maternal FC/BW; fetal abnormalities, irregular skeletal ossification and reduced neonatal BW (0.8-11X HE) 2. Rabbits: decreased fetal BW and increased fetal malformations (irregular ossification and/or skeletal and visceral abnormalities) at <1X HE	Once daily 0.6–1.8 mg (SQ)	A: Tmax 8-12 hrs (T2D) and 11hrs (Obesity) (BA 55%) D: Vd 13 L (T2D) and 20-25 L (Obesity) (plasma albumin-bound>98%) M: protein catabolism E: CL 1-2 L/h (T2D) and 0.9-1.4 L/h (Obesity); t½ 13 hrs; excretion via urine and feces (no parent compound) ***Note: PK of liraglutide not affected when administered as XULTOPHY 100/3.6.***	GI-related: nausea, diarrhea, vomiting, decreased appetite, dyspepsia, constipation; others: immunogenicity-related urticaria (0.8%)
	Saxenda		2014 NDA206321 (Novo Nordisk)	Obesity										Once daily 0.6-3.0 mg (SQ)		GI-related: nausea, diarrhea, constipation, vomiting, dyspepsia, abdominal pain, upper abdominal pain, pyrexia, and gastroenteritis; others: injection site reactions, headache, hypoglycemia, fatigue, dizziness, increased lipase
	Xultophy 100/3.6	liraglutide + insulin degludec (Tresiba®)	2016 NDA208583 (Novo Nordisk)	T2D	Combination: Mono-agonist GLP-1R + insulin degludec			Sequence modification + covalent attachment of fatty acid + long-acting insulin						Once daily 10-50 units insulin degludec and 0.36-1.8 mg liraglutide (SQ)		GI-related: nausea, diarrhea; others: nasopharyngitis, headache, increased lipase, upper respiratory tract infection, immunogenicity-related urticaria (0.8%)
Human GLP-1 analogs (DPP-4-resistant & fusing to carrier moiety); *long-acting*	Tanzeum	albiglutide	2014 BLA125431 (GSK)	T2D	Mono-agonist GLP-1R		97%	Sequence modification + two GLP-1 analog in tandem fused to human albumin	PK in mice and NHPs: ADA in mice (day 8) and in NHPs (day 15); limited data on Cmax/AUC and A: BA >38% (mice) and >50% (NHPs) E: t½ 8-12 hrs (mice) and 60 hrs (NHPs) ***Tissue distribution, metabolic, and excretion pathways not conducted in accordance with Biologics guidance***	CNS, CVS, and respiratory functions in NHPs: No adverse effects at the clinical exposure	Pivotal Tox in 12 months NHPs (only): (ADA response diminished drug exposure and led to type 3 hypersensitivity reactions in mice) NHPs: No significant findings, including pancreatitis (observed in patients post-treatment)	*Carci in rodents could not be assessed due to rapid development of drug-clearing, anti-drug antibodies (ADAs), and no genotoxicity conducted for Albiglutide as a recombinant protein*	DART in mice (limit dosing period < 15 days to minimize ADA effects): Mice: embryo-fetal lethality and malformations with maternal toxicity (reduced FC/BW); increased clinical signs in offspring; No teratogenic findings	Once weekly 30 or 50 mg (SQ)	A: Tmax 3-5 days D: Vd 11 L M: protein catabolism E: CL 0.067 L/h; t½ 5 days	GI-related: diarrhea, nausea; others: upper respiratory tract infection, injection site reaction, cough, back pain, arthralgia, sinusitis, influenza
	trulicity	dulaglutide	2014 BLA125469 (Eli Lilly)	T2D	Mono-agonist GLP-1R		90%	Sequence modification + two GLP-1 analog linked to human mAb IgG4-Fc	PK in mice, rats, rabbits, NHPs: Limited data on Cmax/AUC and E: t½ 7 days in NHPs similar to 5 days in T2D patients; not calculated for mice/rats/rabbits	CNS, CVS, and respiratory functions in vitro and in NHPs: 1. human embryonic kidney (HEK) cells: hERG current inhibition (-33%) at the highest conc. 2. Telemetered NHPs: increases in heart rate, QTcB, and left ventricular inotropic state (dP/dtmax) w/o effects on BP	Pivotal Tox in Zucker diabetic fatty (ZDF) rats and NHPs for 3 and 12 months: 1. ZDF rats: increase in amylase (12-33%) at all doses (1-13X HE) w/o microscopic pancreatic inflammatory correlation; increased interlobular ductal epithelium, acinar atrophy/inflammation 2. NHPs: no pancreatic inflammation or proliferation in thyroid C-cells (200X HE)	Carci in 2-year rats and 6-month transgenic mice: 1. Rats: significant increase in thyroid C-cell tumors (adenomas and/or carcinomas) in M/F (63X MRHD) 2. RasH2 mice: no tumorigenicity 3. No genotoxicity conducted for Dulaglutide as a recombinant protein	DART in rats and rabbits: 1. Rats: prolonged diestrus and decrease in corpora lutea/implantation sites and viable embryos/fetuses; fetal malformations and skeletal variations; reduced neonatal BW and neurotoxicity in female pups 2. Rabbits: fetal malformations and skeletal variations (13-17X HE)	Once weekly 0.75–4.5 mg (SQ)	A: Tmax 24-72 hrs (BA 47-65%) D: Vd 3.09-5.98 L M: protein catabolism E: CL 0.142 L/h; t½ 5 days	GI-related: nausea, diarrhea, vomiting, abdominal pain, decreased appetite
	Ozempic	semaglutide	2017 NDA209637 (Novo Nordisk)	T2D	Mono-agonist GLP-1R		94%	Sequence modification + covalent attachment of fatty acid	PK in mice, rats, rabbits, minipigs, NHPs: A: Tmax 3-4 hrs in mice/rats, 12-24 hrs in NHPs/minipigs (BA 86% in NHPs) D: Vd 0.2 L/kg in NHPs; plasma albumin-bound>99% in all species M: proteolytic cleavage (peptide), β-oxidation (fatty diacid) and amide hydrolysis E: t½ 7-54 hrs (mouse<rat<NHP); excretion via urine/feces (1% parent compound in rats feces and urine) ***Wegovy and Rybelsus cross-reference Ozempic applications in nonclinical PK/tox studies***	CNS, CVS, respiratory, and renal functions in rats, rabbits, and NHPs: No adverse effects at the clinical exposure	Pivotal Tox in mice, rats, and NHPs for 3, 6, and 12 months A. Mice: liver necrosis, thyroid focal C-cell hyperplasia, C-cell nests, and dilated utimobranchial ducts at clinical exposure 2. Rats: no adverse findings 3. NHPs: myocardial vacuolation and degeneration, ECG abnormalities at 17-27X clinical exposure	Carci in 2-year rats and mice: 1. Rats: significant increase in C-cell adenomas (M/F) and C-cell carcinomas (M) at clinical exposures 2. Mice: significant increase in thyroid C-cell adenomas and a numerical increase in C-cell carcinomas at clinical exposures 3. Not mutagenic or clastogenic in a standard battery of genotoxicity tests	DART in rats, rabbits, and NHPs: 1. Rats: decrease in maternal BW, embryo-fetal mortality, growth retardation, skeletal and visceral malformations (1X HE) 2. Juvenile rats (PD21-97): reduction in FC/BW and delayed sexual maturation (1X HE) 3. Rabbits: marked maternal BW loss, increased post-implantation loss, skeletal and visceral malformations (1X HE) 4. NHPs: marked maternal BW loss (1X HE); early pregnancy losses (3X HE); delayed fetal development and malformations (>5X HE)	Once weekly 0.5–2.0 mg (SQ)	A: Tmax 1-3 days (SQ) and 1 hr (Oral) (BA 89% post-SQ and 0.4-1% post-Oral) D: Vd 12.5 L (SQ) and 8.0 L (Oral) (plasma albumin-bound>99%) M: proteolytic cleavage (peptide) and β-oxidation (fatty acid) E: CL 0.05 L/h (SQ) and 0.04 L/h (Oral); t½ 7 days; excretion via urine and feces (3% parent compound in urine)	GI-related: nausea, vomiting, diarrhea, abdominal pain, constipation
	Wegovy		2021 NDA215256 (Novo Nordisk)	Obesity										Once weekly 0.25–2.4 mg (SQ)		GI-related: nausea, diarrhea, vomiting, constipation, abdominal pain, abdominal distension, gastroenteritis, gastroesophageal reflux disease, dyspepsia; others: headache, fatigue, dizziness, eructation, hypoglycemia, flatulence, nasopharyngitis
	Rybelsus	semaglutide / SNAC (oral absorption enhancer; *short-acting*)	2019 NDA213051 (Novo Nordisk)	T2D										Once daily 3, 7, 14 mg (oral)		GI-related: nausea, abdominal pain, diarrhea, decreased appetite, vomiting constipation
Human GIP/GLP-1 analogs (DPP-4-resistant & attachment of fatty acid); *long-acting*	Mounjaro	tirzepatide	2022 NDA215866 (Eli Lilly)	T2D	Dual-agonist GIPR and GLP-1R (efficacy >> mono-agonist)		shares 100% homology with GIP E3- 112 (10 AAs), and 100% homology with GLP-1 A29-S39 (11 AAs)	Sequence modification + covalent attachment of fatty acid	PK in mice, rats, rabbits, NHPs: A: Tmax 4-24 hrs (BA 83% in NHPs) D: plasma albumin-bound 99% in NHPs and 98% in rats; small amount cross BBB M: proteolytic cleavage, β-oxidation and amide hydrolysis E: t½ 55-103 hrs; excretion via urine/feces (no parent compound) ***Zepbound cross-reference Mounjaro applications nonclinical PK/tox studies***	CNS, CVS, and respiratory functions in NHPs: Increases in heart rate and MAP at clinical exposure; no effects on QTc intervals and hERG current	Pivotal Tox in rats and NHPs for 1 and 6 months: 1. Rats: reductions in FC/BW; pancreatic lobular atrophy; thyroid C-cell hyperplasia; decreases in splenic extramedullary hematopoiesis 2. NHPs: reductions in FC/BW; pancreatic lobular atrophy	Carci in 2-year rats and 6-month transgenic mice: 1. Rats: significant increase in thyroid C-cell tumors (adenomas and carcinomas) in M/F at clinical exposure 2. RasH2 mice: no tumorigenicity 3. No genotoxicity in a rat bone marrow micronucleus assay	DART in rats and rabbits: 1. Rats: maternal toxicity (reduced FC/BW; 1X HE); prolonged diestrus and decreased corpora lutea/implantation sites and viable embryos; reduction in pup weight and reduced/delayed fetal growth and weight; skeletal/visceral malformations in fetuses 2. Rabbits: maternal toxicity (reduced FC/BW; 1X HE); increased fetal loss/abortion	Once weekly 2.5–15 mg (SQ)	A: Tmax 8-72 hrs (BA 80%) D: Vd 10.3 L (T2D) and 9.7 L (Obesity) (plasma albumin-bound 99%) M: proteolytic cleavage, β-oxidation and amide hydrolysis E: CL 0.061 L/h (T2D) and 0.056 L/h (Obesity); t½ 5 days; excretion via urine and feces (no parent compound)	GI-related: nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, abdominal pain
	Zepbound		2023 NDA217806 (Eli Lilly)	Obesity										Once weekly 2.5–15 mg (SQ)		GI-related: nausea, diarrhea, vomiting, constipation, abdominal pain, dyspepsia, gastroesophageal reflux disease; others: injection site reactions, fatigue, hypersensitivity reactions, eructation, hair loss

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