GLP-1 derivatives as novel compounds for the treatment of type 2 diabetes: selection of NN2211 for clinical development

L. Bjerre Knudsen*, H. Agerso, C. Bjenning, S. Bregenholt, R.D. Carr, C. Godtfredsen, J.J. Holst⁺, P.O. Huusfeldt, M.O. Larsen, P.J. Larsen#, P.F. Nielsen, U. Ribel, B. Rolin, J. Romer, J. Sturis, M. Wilken and P. Kristensen

Novo Nordisk, Novo Park, DK-2760 Maaloev, Denmark;
⁺Dept. of Medical Physiology, University of Copenhagen, DK-2200 Copenhagen, Denmark; #Present address: Lab. Obesity Research, CCRB, DK-2760 Ballerup, Denmark.
*Correspondence

CONTENTS

Introduction

Current drugs for treatment of type 2 diabetes are classified into four major categories: insulin secretagogues (sulfonylureas and the shorter acting glinides), biguanides, insulin sensitizers and insulin (1). The first three groups are orally active but are of limited efficacy. Insulin is very effective but has to be dosed four times daily for optimal efficacy, thus presenting the risk of serious hypoglycemia to the patient. Furthermore, type 2 diabetes is most commonly associated with obesity, and of the four drug groups listed, only the biguanides do not cause increases in body weight. There is, therefore, an increasing awareness of the need for new efficacious drugs for the treatment of type 2 diabetes, especially drugs that do not lead to an increase in body weight. Glucagon-like peptide-1 (GLP-1) is a peptide hormone derived from proglucagon which was discovered in 1983 (2, 3). GLP-1 was first described as an incretin, a substance released from the gastrointestinal system upon ingestion of food, promoting glucose-dependent insulin release from the pancreatic β-cells. Later, GLP-1 was found to also lower plasma glucagon in a glucose-dependent manner, decrease the rate of gastric emptying, promote fullness/satiety and stimulate insulin biosynthesis, as well as proliferation of β-cells. All of these effects taken together position GLP-1 as an obvious drug candidate for the treatment of type 2 diabetes. Apart from the food intake lowering effect, the glucagonostatic effect is particularly interesting as type 2 diabetic patients are characterized by increased plasma glucagon levels, which again lead to an increased hepatic glucose output (4, 5).

The natural hormone GLP-1 is found as both GLP-1(7-37) and GLP-1(7-36)amide. It is metabolized by dipeptidyl peptidase IV (DPP-IV) and rapidly cleared by the kidneys (6, 7). The primary metabolite, GLP-1(9-37) or GLP-1(9-36)amide, may even act as an antagonist (8). The plasma half-life of GLP-1 after i.v. administration is less than 2 min and 1-2 h after s.c. administration (9). The dynamic half-life of GLP-1 has been estimated to be 3 h (10). Thus, the natural hormone is not very useful as a drug. No small-molecule agonists have been described for any members of the glucagon-secretin G-protein coupled receptor family, to which the GLP-1 receptor belongs. Thus, in order to make a GLP-1-based drug, one must either make a protracted formulation of the natural hormone, design analogs or derivatives with improved pharmacokinetic properties or find a non-peptide agonist.

This review describes the biological aspects of GLP-1 and gives a detailed description of a series of GLP-1 derivatives designed for once-daily administration.

Mechanism of action of GLP-1

GLP-1 is an incretin, responsible for the difference in blood glucose levels obtained after oral as compared to

intravenous administration of the same amount of glucose (11-14). Upon ingestion of a meal, GLP-1 is released from the L-cells in the intestine and stimulates insulin release via specific receptors on pancreatic β-cells.

The GLP-1 receptor was cloned in 1992 (15) and has been shown to be present in numerous tissues with the highest expression levels in the β- and δ-cells of the pancreas and in the lungs (16). Only one subtype is known. The receptor has also been found in parts of the gastrointestinal tract and in many regions in the CNS, including the hypothalamic regions, as well as specific areas in the brain stem.

Equally important to the insulinotropic action, GLP-1 also potently inhibits glucagon secretion (17-20). The mechanism by which GLP-1 exerts its glucagonostatic effect is not fully understood. It has been suggested to be paracrine, via neighboring somatostatin cells. Because of the combination of increased insulin and decreased glucagon secretion, hepatic glucose production is efficiently decreased (21). In spite of the insulinotropic effect, GLP-1 infusions carried out during ingestion of a meal actually result in diminished insulin responses. This is due to an inhibition of gastric emptying effectively reducing the delivery rate of ingested nutrients to the absorptive segments of the GI tract (22).

GLP-1 has been investigated in a substantial number of small clinical trials and has been shown to efficiently lower blood glucose in patients with type 2 diabetes and also in patients with poor metabolic control, referred to as secondary failures to sulfonylurea treatment (9-14). GLP-1 is also capable of lowering blood glucose in type 1 diabetic patients without residual beta-cell secretory capacity (23, 24), reflecting its effects on lowering of plasma glucagon and inhibition of gastric emptying. Indeed, glucagon antagonism alone has been suggested as an alternative treatment for type 2 diabetes but no drugs have reached the market yet.

One study has suggested that the effect of GLP-1 can decline overnight, perhaps as a result of receptor desensitization (25). However, these results are in contrast to another study which showed that a 7-day infusion of GLP-1 lowered blood glucose levels for the entire duration of the study (26, 27).

Because of the glucose-dependent nature of the insulinotropic and glucagonostatic actions of GLP-1, the glucose lowering effect of this hormone is self-limiting and, therefore, it does not cause serious hypoglycemia regardless of dose (28). The mechanism underlying the glucose dependency is closely related to the glucose signaling events being dependent on a high ATP/ADP ratio (29). Numerous studies in the literature, where GLP-1 has been infused or injected subcutaneously in humans, support the glucose dependency of GLP-1's actions (9-14, 23, 25). However, there are some reports that GLP-1 can lower blood glucose to below normoglycemia (30, 31). This ability of GLP-1 to transiently lower blood glucose to subnormal levels is a natural consequence of its effect on insulin secretion. The inactiva-

tion time for insulin is considerable, and after GLP-1 stimulation there may be enough insulin around (and enough activated insulin receptors) to lower blood glucose temporarily, even if secretion of new insulin has ceased because of the falling glucose levels. The overall conclusion, therefore, is that GLP-1 can cause blood glucose to decrease temporarily to below normal, but never leads to profound and lasting hypoglycemia.

Apart from its direct effect on insulin secretion, GLP-1 has been shown to increase the rate of insulin biosynthesis (32, 33) and to restore the failing ability of the beta-cell to respond to glucose in old rats (34-36). Thus, it is speculated that GLP-1 may prevent the transition from IGT to full-blown diabetes (37), presumably because β-cell function is preserved. Also, several publications now show a direct effect of GLP-1 compounds on growth and proliferation of β-cells in animals (38-40), as well as an ability to prevent apoptosis in β-cells (41). GLP-1 has even been found to be able to cause differentiation of pancreatic stem cells into functional β-cells (42).

GLP-1 has also been reported to exert peripheral effects by promoting glucose uptake and glycogen storage in fat cells, skeletal muscle and liver cells in rats (43). A few studies in humans have confirmed that there may be a peripheral effect (44, 45) while others have not (46, 47). Most likely, if this effect exists, it is quantitatively unimportant.

All of the effects described above are aimed at directly lowering blood glucose. However, GLP-1 in peripheral circulation has also been shown to lower food intake in both rodents and humans, indirectly leading to improved glucose control via loss of body weight (48-53). Several receptors may be involved in the food intake lowering effect. First, centrally acting GLP-1 has been suggested to have a role as a physiological satiety factor (53-57) via receptors localized in arcuate hypothalamic areas. However, it has been shown that these receptors are probably not involved in mediating the food intake lowering effect of peripherally administered GLP-1 (52). Binding sites in the area postrema and the subfornical organ have been shown to be accessible for GLP-1 in the peripheral circulation, and these represent likely sites for mediating the food intake effect of peripheral GLP-1 compounds (58). As mentioned above, GLP-1 inhibits gastric emptying, and the vagus nerve has been shown to be involved in mediating this effect (22, 59-62). The areas in the brainstem containing the GLP-1 receptors are known to receive afferent inputs from gastrointestinal organs. Thus, the most likely mechanism for the food intake lowering effect of a peripherally administered GLP-1 compound that does not pass the blood-brain barrier is that a sensation of fullness is obtained via small amounts of receptor in the intestine which then projects via the vagus nerve to receptors in the area postrema and the subfornical organ or directly via receptors in the blood-brain barrier free areas of the CNS.

Obese subjects have been shown to have an attenuated GLP-1 release in response to meals (63, 64), suggesting that a decreased peripheral GLP-1 signal may

contribute to the development of obesity. Also, type 2 diabetes patients have been shown to have a reduced GLP-1 release in response to food ingestion (65) and they have a defect in their response to the other incretin hormone, GIP (11). Thus, there is a very good rationale for treating type 2 diabetes and obesity with a GLP-1-based drug as a replenishment treatment.

A significant inhibitory effect of GLP-1 on water intake has been observed together with profound stimulation of diuresis in rats (54). The profound diuretic response to acute GLP-1 administration is due to natriuresis. However, chronic administration of a GLP-1 derivative was shown not to lead to disturbed water homeostasis in rats (52). In humans, GLP-1 does not acutely affect water homeostasis (66).

Last, GLP-1 potently inhibits pentagastrin and meal-induced gastric acid secretion and pancreatic enzyme secretion (59, 60). Along with the inhibited gastric emptying, these effects of GLP-1 are most likely mediated vagally (61). The effect of GLP-1 gastric acid secretion may also point to a role for GLP-1 in protection against gastric ulceration.

A recent very comprehensive review has a thorough description of the biology of GLP-1 (67).

In conclusion, the mode of action of GLP-1 seems to be ideal for the treatment of type 2 diabetes, especially obese type 2 diabetes patients. GLP-1 compounds glucose-dependently stimulate insulin secretion and inhibit glucagon secretion, decrease gastric emptying and mediate increased fullness and/or appetite, and directly stimulate growth and rescue of pancreatic β-cells. With this important spectrum of effects of GLP-1, it is conceivable that a GLP-1-based compound could potentially be more effective than any of the current blood glucose lowering drugs available today.

Desired pharmacodynamic profile of an effective GLP-1 drug

Several studies have shown that GLP-1 can normalize blood glucose in patients and remains very effective in the so-called sulfonylurea failure patients, but it has a very short duration of action. It has been suggested that repeated subcutaneous administration of GLP-1 (9-10, 25) or buccal tablets (68) might be an effective treatment. However, a study by Larsen et al. (26) shows that a long dynamic half-life is needed in order to maintain good glucose control on a GLP-1-based drug. In this study, patients were administered GLP-1 by infusion for either 16 h or 24 h a day for 1 week. Patients in the 24-h infusion group had a much better glucose control than those in the 16-h infusion group (26). In patients in the 16-h infusion group, blood glucose rapidly reverted to preinfusion levels after GLP-1 infusion. Thus, the difference between these two groups strongly indicates that GLP-1 has to be present in an effective dose at all times. At least three daily administrations of natural GLP-1 by buccal or s.c. administration would be needed in order to obtain this kind of pharmacodynamic profile.

As mentioned above, GLP-1 is metabolized rapidly by DPP-IV and the major metabolite, GLP-1(9-36)amide or GLP-1(9-37) is inactive or may even act as an antagonist (8). Thus, analogs of GLP-1 stabilized against metabolic breakdown have been proposed as possible drugs (69-72). However, as GLP-1 is also cleared very rapidly from the kidneys, such drugs would only have half-lives of around 5 min after i.v. administration (69). Even though s.c. administration would improve the dynamic half-lives of such compounds, probably to a range of 3-5 h (72, 73), they still require a tremendous formulation challenge if multiple daily dosing is to be avoided.

The only known side effect of GLP-1 treatment is nausea, occurring at plasma concentrations high enough to markedly slow gastric emptying. Thus, the most optimal pharmacokinetic profile of a GLP-1 drug from this perspective would again be a long half-life with as few as possible peak concentrations. Thus, compounds administered several times a day have a disadvantage over compounds with only once-daily administration.

Derivatizing GLP-1 with long fatty acids has been shown to result in half-lives exceeding 10 h in healthy humans as well as type 2 diabetic patients after s.c. administration. Such derivatives of GLP-1 could be dosed once daily and provide active plasma concentrations throughout the day.

Derivatives of GLP-1 for once-daily administration

Fatty acid derivatization has been used successfully to protract the action of insulin by facilitating binding to plasma albumin (74-77). The same principle has been used to design derivatives of GLP-1 with half-lives longer than 10 h, thereby being optimal for once-daily administration (78). Fatty acids or fatty diacids, optionally extended with a "spacer" between the epsilon-amino group of the lysine side chain and the carboxyl group of the fatty acid, were used. Acylation with simple fatty acids increases the net negative charge of the resulting molecule with one (by blocking the epsilon-amino group of the lysine), whereas peptides acylated with a L-glutamoyl-spacer or with diacids provides a further increase of the negative charge. The addition of a negative charge to the acylated molecule is expected to improve solubility at physiological pH.

The amino acid sequence of GLP-1 can be seen in Figure 1. GLP-1(7-37) and close analogs thereof, as well as an extended molecule, were derivatized on position 8, 18, 23, 26, 27, 34, 36 or 38 with fatty acids and optionally a spacer (Table I). The structure-activity relationship (SAR) of the compounds was investigated using a functional assay employing the cloned human GLP-1 receptor expressed in baby hamster kidney cells. All compounds tested were full agonists and were shown to selectively activate the GLP-1 receptor. Table II shows plasma half-lives after s.c. administration to pigs for a selection of very potent compounds **4**, **5**, **7**, **8**, **18**, **20** and **21**. All compounds acylated with a fatty acid equal to or longer than

His[7]-Ala-Glu-Gly[10]-Thr-Phe-Thr-Ser-Asp[15]-Val-Ser-Ser-Tyr-Leu[20]-Glu-Gly-Gln-Ala-Ala[25]-Lys-Glu-Phe-Ile-Ala[30]-Trp-Leu-Val-Lys-Gly-Arg-Gly[37]

Fig. 1. Amino acid sequence of GLP-1.

12 carbon atoms were considerable protracted compared to native GLP-1, which had a half-life after s.c. administration of only 1.2 h. Bioavailability was measured for selected compounds and was shown to be on the order of 50% and above. Figure 2 illustrates the dramatic difference in plasma half-lives between GLP-1 and three potent acylated compounds **5**, **7** and **8**.

Site of acylation

Many different positions in the C-terminal part of GLP-1 could be derivatized with quite long fatty acids, visualized with compounds **3-9** (EC_{50} 30-121 pM) without affecting the potency. Binding affinity was not measured for these compounds as they all bind to albumin as part of their mechanism of protraction and it has not been possible to set up a reproducible binding assay without albumin. Derivatizing amino acids in the N-terminal part of the peptide, as exemplified in compound **2** (1260 pM), led to a substantial loss of potency. This is in agreement with earlier findings showing the importance of the N-terminal region for affinity (79).

Compounds derivatized on lysine 26

The potency of the compounds was comparable when looking at a series of different length diacids (**14**, **15**, Table I) or fatty acids with the same spacer (**5**, **16-18**). Within the γ-Glu spacer monoacid series (**5**, **16-18**), derivatization with a C18 acid (**16**, 194 pM) led to a significant loss of activity compared to C16 (**5**, 68 pM), C14 (**17**, 22 pM) and C12 (**18**, 27 pM). Within the diacid series (**14**, **15**), the diacid could be no longer than a C14 (**15**, 72 pM) before a loss in potency (**14**, 154 pM), compared to the γ-Glu spacer monoacid series (**17**, **18**, 22-27 pM) was seen. In earlier studies from our group and others, attempts were made to modify the amino terminus of GLP-1 in order to make the molecule more resistant to enzymatic breakdown (69, 80-81). Desamino His[7] represents one of the more potent suggestions to a modification giving metabolic stability (81). Nevertheless, as seen when comparing **19** (687 pM) to **5** (68 pM), considerably more potent compounds could be obtained by not modifying the N-terminus when a combination with acylation was desired. This could be caused both by the position of the fatty acid and by the modified histidine.

Compounds derivatized with different spacers

The γ-Glu spacer is optically active. Thus, it presents a greater analytical challenge when upscaling the compounds for good manufacturing production guidelines. We therefore investigated other spacers without optical

Table I: GLP-1 compounds and their potency measured using the cloned human GLP-1 receptor expressed in baby hamster kidney cells.

Cpd.	Parent peptide	Acyl site	Acyl substituent	Potency (EC_{50}, pM)
1	GLP-1(7-37)	-	None	55 ± 19
2	K8R26,34-GLP-1(7-37)	K8	γ-Glu-C16	1260 ± 210
3	K18R26,34-GLP-1(7-37)	K18	γ-Glu-C16	35.2 ± 6.2
4	K23 R26,34-GLP-1(7-37)	K23	γ-Glu-C16	30.1 ± 3.3
5	R34-GLP-1(7-37)	K26	γ-Glu-C16	61.0 ± 7.1
6	K27R26,34-GLP-1(7-37)	K27	γ-Glu-C16	36.3 ± 0.3
7	R26-GLP-1(7-37)	K34	γ-Glu-C16	121 ± 26
8	K36R26,34-GLP-1(7-36)	K36	γ-Glu-C16	36.4 ± 2.1
9	R26,34-GLP-1(7-38)	K38	γ-Glu-C16	53.0 ± 2.8
14	R34-GLP-1(7-37)	K26	C16-diacid	154 ± 66
15	R34-GLP-1(7-37)	K26	C14-diacid	72 ± 0.7
16	R34-GLP-1(7-37)	K26	γ-Glu-C18	194 ± 24
17	R34-GLP-1(7-37)	K26	γ-Glu-C14	22.0 ± 7.1
18	R34-GLP-1(7-37)	K26	γ-Glu-C12	27.3 ± 8.4
19	Des-amino-H7R34-GLP-1(7-37)	K26	γ-Glu-C16	687 ± 129
20	R34-GLP-1(7-37)	K26	GABA-C16	84.4 ± 22.1
21	R34-GLP-1(7-37)	K26	β-Ala-C16	113 ± 3
22	R34-GLP-1(7-37)	K26	Iso-Nip-C16	410 ± 120

Abbreviations used for acyl groups in lysine-*N*-ε-acylated peptides: γ-Glu-C12 = γ-L-glutamoyl(*N*-α-dodecanoyl); γ-Glu-C14 = γ-L-glutamoyl(*N*-α-tetradecanoyl); γ-Glu-C16 = γ-L-glutamoyl(*N*-α-hexadecanoyl); γ-Glu-C18 = γ-L-glutamoyl(*N*-α-octadecanoyl); C14-diacid = ω-carboxytridecanoyl; C16-diacid = ω-carboxypentadecanoyl; GABA-C16 = γ-amino- butyryl(*N*-γ-hexadecanoyl); Iso-Nip-C16 = 1-(hexadecanoyl)piperidyl-4-carboxy. Data are given as mean ± SD of 2 individual experiments with triplicate samples. (Reprinted in part with permission from J Med Chem 2000, 43; 1664-1669. Copyright 2000 American Chemical Society.)

Table II: Plasma half-lives in pigs of GLP-1 and selected potent acylated compounds.

Cpd.	Plasma t½ (h)
1(GLP-1)	1.2
4	20 ± 2
5	14 ± 2
7	13
8	12 ± 1
18	15 ± 3
20	31 ± 4
21	8.8 ± 1

The half-lives were calculated from individual pigs after a single s.c. injection. Each compound was injected in 2 pigs. Data are shown as mean ± SD. For (**7**), half-life could only be calculated from 1 pig. (Reprinted in part with permission from J Am Chem 2000, 43: 1664-1669. Copyright 2000 American Chemical Society.)
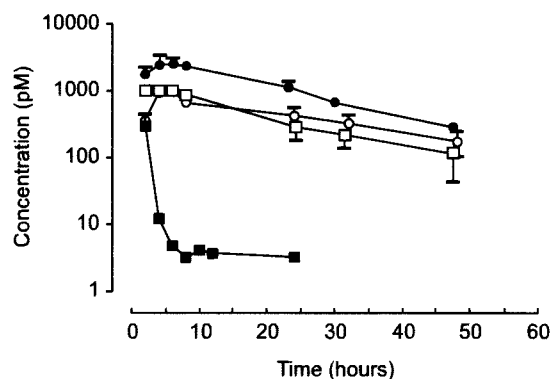

Fig. 2. Pharmacokinetic profile of selected compounds after s.c. administration to pigs. **1** (GLP-1) (■), **5** (◡), **7** (●) and **8** (▫). Two pigs were dosed with compounds after which the immunoassay was performed in duplicate. Data are expressed as mean ± SD. (Reprinted with permission from J Med Chem 2000, 43: 1664-1669. Copyright 2000 American Chemical Society.)

activity. A GABA spacer (**20**, 84 pM) gave a compound with equal affinity to the γ-Glu spacer (**5**, 68 pM). A β-Ala spacer reduced the activity slightly (**21**, 113 pM) and a piperidyl-4-carboxy spacer resulted in a 6-fold lower activity (**22**, 410 pM).

As described above, several compounds had half-lives making them suitable for once-daily administration. Compound **5**, γ-L-glutamoyl(N-α-hexadecanoyl)-Lys[26], Arg[34]-GLP-1(7-37) was selected as the best compound for several reasons. A γ-L-Glu spacer was preferred because it gave the most potent compound. Position 26 or 34 were the most preferred amino acids to derivatize because they were natural lysines and could thus be derivatized easily and without introducing any potential immunogenic changes in the amino acid sequence. Position 26 gave the most potent compound. Furthermore, acylation at position 26 gave the most metabolical-

ly stable compound. Compound **5** had an *in vitro* half-life of 20 h, whereas compounds derivatized on position 34 (**7**) and position 36 (**8**) had *in vitro* half-lives of 6.3 and 6.9 h, respectively (82). For comparison, GLP-1(7-36)amide had an *in vitro* half-life of 0.12 h. Amino acid substitutions in position 8 can give better metabolic stability against DPP-IV. However, since quite a substantial protection against DPP-IV was obtained by acylation alone, and since any amino acid substitution poses a risk of immunogenicity, and since compound **5** was equipotent with GLP-1 and had the half-life required to be dosed once daily, compound **5** was selected for clinical development under the name of NN2211.

The long half-life in pigs, adequate for once-daily administration, has as mentioned above been confirmed in man, where the half-life was determined to be 12 ± 2 h following a single injection to healthy humans and 10.0 ± 3.5 h following a single injection to type 2 diabetic subjects (83-84).

Biological characterization of NN2211

As shown above, NN2211 was a full agonist with equal potency to GLP-1 on the cloned human GLP-1 receptor. Its mechanism of protraction involves binding to albumin, metabolic stability towards DPP-IV and slow release from the injection site. Because of the binding to albumin, NN2211 appears less potent than GLP-1 in the presence of high concentrations of albumin. NN2211 has been shown to be selective, as it has no activity on the very closely related glucagon receptor, and also did not bind to any receptors in a broad Panlabs receptor binding screen (data not published).

NN2211 has been studied extensively in pigs, representing the only model where s.c. administration normally results in pharmacokinetic profiles comparable to those of human subjects. In STZ-induced glucose intolerant minipigs, clamp experiments showed that NN2211 increased glucose utilization while at the same time increasing insulin secretion and inhibiting glucagon release, both in a glucose-dependent manner. Gastric emptying was decreased as well (85). In STZ-induced diabetic minipigs, 0.004 mg/kg/day (0.28 mg/75 kg) NN2211 lowered blood glucose to near normal levels after 2-4 weeks of once-daily administration and normalized prandial glucose tolerance (86).

In order to obtain full efficacy in rodents, all pharmacology studies have been carried out with higher doses than in pigs and monkeys. Rodents, in general, seem to have a lower sensitivity to GLP-1 compounds and a more aggressive metabolism of GLP-1.

In normal rats, 0.2 mg/kg twice-daily NN2211 has been shown to significantly decrease body weight by 15%, inhibit food and water intake and stimulate diuresis (52). In subchronic experiments, water intake was compensatorily increased to account for the increased diuresis. The mechanism for the decreased food intake apparently does not involve hypothalamic GLP-1 receptors, as

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.