Effects of Olanzapine Combined With Samidorphan on Weight Gain in Schizophrenia: A 24-Week Phase 3 Study

Christoph U. Correll, M.D., John W. Newcomer, M.D., Bernard Silverman, M.D., Lauren DiPetrillo, Ph.D., Christine Graham, Ph.D., Ying Jiang, Ph.D., Yangchun Du, Ph.D., Adam Simmons, M.P.H., Craig Hopkinson, M.D., David McDonnell, M.D., René S. Kahn, M.D., Ph.D.

Objective: A combination of olanzapine and the opioid receptor antagonist samidorphan is under development for the treatment of schizophrenia and bipolar I disorder. The single-tablet combination treatment is intended to provide the efficacy of olanzapine while mitigating olanzapine-associated weight gain. In this phase 3 double-blind trial, the authors evaluated the weight profile of combined olanzapine/samidorphan compared with olanzapine in patients with schizophrenia.

Methods: Adults (ages 18 55 years) with schizophrenia were randomly assigned to receive either combination treatment with olanzapine and samidorphan or olanzapine treatment for 24 weeks. Primary endpoints were percent change from baseline in body weight and proportion of patients with ≥10% weight gain at week 24. The key secondary endpoint was the proportion of patients with ≥7% weight gain. Waist circumference and fasting metabolic laboratory parameters were also measured.

Results: Of 561 patients who underwent randomization (olanzapine/samidorphan combination, N=280; olanzapine, N=281), 538 had at least one postbaseline weight assessment. At week 24, the least squares mean percent weight change from baseline was 4.21% (SE=0.68) in the olanzapine/samidorphan group and 6.59% (SE=0.67) in the olanzapine group (the difference of 2.38% [SE=0.76] was significant). Significantly fewer patients in the olanzapine/samidorphan combination group compared with the olanzapine group had weight gain ≥10% (17.8% and 29.8%, respectively; number needed to treat [NNT]=7.29; odds ratio=0.50) and weight gain ≥7% (27.5% and 42.7%, respectively; NNT=6.29; odds ratio=0.50). Increases in waist circumference were smaller in the olanzapine/samidorphan combination group compared with the olanzapine group. Schizophrenia symptom improvement was similar between treatment groups. Adverse events (in ≥10% of the groups) in the olanzapine/samidorphan and olanzapine groups included weight gain (24.8% and 36.2%), somnolence (21.2% and 18.1%), dry mouth (12.8% and 8.0%), and increased appetite (10.9% and 12.3%). Metabolic changes were small and similar between treatments.

Conclusions: Olanzapine/samidorphan combination treatment was associated with significantly less weight gain and smaller increases in waist circumference than olanzapine and was well tolerated. The antipsychotic efficacy of the combination treatment was similar to that of olanzapine monotherapy.

Am J Psychiatry 2020; 177:1168 1178; doi: 10.1176/appi.ajp.2020.19121279

Mental disorders are a leading cause of ill health and disability worldwide (1). Schizophrenia affects 2.4 million people in the United States (2) and is associated with a 3.7-fold increased mortality risk (3). Antipsychotics, including olanzapine, are the cornerstone of treatment of schizophrenia. In long-term effectiveness studies, olanzapine treatment was associated with lower rates of hospitalization for disease exacerbation (4, 5), higher rates of remission (6), and consistently longer time to all-cause discontinuation (4, 5, 7). Despite olanzapine's robust efficacy, the associated risk of significant weight gain and metabolic sequelae (4, 8) has limited its overall clinical utility (9).

Antipsychotic-associated weight gain reduces adherence and leads to treatment switches (10, 11), placing patients at significant risk of relapse, hospitalization, and disease progression (12). In patient populations already predisposed to shortened lifespan and cardiometabolic risks, weight gain exacerbates this risk. Weight gain also profoundly affects quality of life, psychosocial adaptation, body image, and self-esteem (13, 14), an impact superimposed on the challenges accompanying a psychiatric diagnosis, including stigma and social isolation (15).

Evidence suggests that opioid receptor antagonists may mitigate medication-associated weight gain and/or metabolic dysregulation (16–19). Samidorphan, a new molecular entity, binds in vitro with high affinity to human μ-, κ-, and δ-opioid receptors and acts as an antagonist at μ-opioid receptors and a

See related feature: **Editorial** *by Dr. Buchanan (p. 1113)*

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

partial agonist at κ- and δ-opioid receptors (20, 21). In vivo, samidorphan functions as an opioid receptor antagonist (22).

A combination of olanzapine and samidorphan administered as a single tablet is under development for treatment of schizophrenia and bipolar I disorder, and it is hypothesized that the combination treatment would be associated with significantly less weight gain than olanzapine monotherapy. Antipsychotic efficacy of the combination treatment has been established in a phase 3 study in patients with an acute exacerbation of schizophrenia (23). In preclinical studies, coadministration of olanzapine and samidorphan was found to attenuate olanzapine-associated weight gain and mitigate several olanzapine-associated metabolic abnormalities, independently of effects on weight (24). In a 12-week phase 2 dose-ranging study in patients with schizophrenia, combined olanzapine/samidorphan treatment resulted in a 37% reduction in weight gain compared with olanzapine (25). Thus, combined olanzapine/samidorphan treatment may have an improved benefit-risk profile compared with olanzapine, providing an important long-term treatment option with antipsychotic efficacy and the benefit of significantly reduced weight gain (23, 26). This 24-week phase 3 study was specifically designed to evaluate the weight profile of combined olanzapine/samidorphan compared with olanzapine at clinically relevant dosages in adults with schizophrenia.

METHODS

Ethics

The study (ClinicalTrials.gov identifier: NCT02694328) was conducted in accordance with the Declaration of Helsinki, 1964, and Good Clinical Practice principles (International Conference on Harmonization, 1997). The study protocol and all amendments were approved by an institutional review board at each study site.

Patients

Patients 18–55 years of age meeting DSM-5 criteria for a primary diagnosis of schizophrenia were enrolled. Patients were required to be outpatients, have a baseline body mass index (BMI) between 18 and 30, and have stable body weight (self-reported change ≤5%) for at least 3 months before study initiation.

Key exclusion criteria included a history of treatment-resistant schizophrenia, <1 year elapsed since initial onset of symptoms, naive to antipsychotic medication, active alcohol or substance use disorders (excluding marijuana/tetrahydrocannabinol), or any clinically significant or unstable medical illness (e.g., diabetes, hypo- or hypertension, thyroid dysfunction, and history of seizure disorder or brain tumor) that might compromise patient safety or study endpoint assessments or interfere with the ability to fulfill study requirements. Opioid agonist use within 14 days of screening, opioid antagonist use within 60 days of screening, or anticipated need for opioid treatment during the study were exclusionary, as was the use of olanzapine in the 60 days before screening. All patients provided written informed consent after receiving a complete description of the study.

Study Design

This was a phase 3 multicenter, randomized, double-blind study conducted in the United States. Candidates were screened within 30 days of randomization; eligible patients were randomly assigned in a 1:1 ratio to receive treatment with either combined olanzapine/samidorphan or olanzapine for 24 weeks (see Figure S1A in the online supplement). Study completers were eligible to enroll in a long-term open-label safety study evaluating treatment with combined olanzapine/samidorphan over 52 weeks (ClinicalTrials.gov identifier: NCT02873208); those who elected not to enroll (or who prematurely discontinued the double-blind study) entered a 4-week safety follow-up period.

Study Treatment

The daily doses of combined olanzapine/samidorphan used in this study (10 mg olanzapine/10 mg samidorphan [10/10] and 20 mg olanzapine/10 mg samidorphan [20/10]) represent the lowest and highest approved maintenance dosages of olanzapine for schizophrenia treatment and the intended therapeutic fixed dosage of samidorphan, representing the optimal weight and safety profile when combined with olanzapine (25, 27).

In general, the use of psychotropic medications other than study drug was prohibited, except for beta-blockers, antihistamines, benzodiazepines, and anticholinergics for akathisia or extrapyramidal symptoms. Patients who were taking other antipsychotic medications at study entry were cross-tapered off these medications and titrated onto either combined olanzapine/samidorphan treatment or olanzapine monotherapy over the course of 2 weeks. In the first week, patients received daily doses of combined olanzapine/samidorphan 10/10 or 10 mg olanzapine. The olanzapine dosage was increased to 20 mg/day beginning at week 2. At the end of week 2, 3, or 4, the olanzapine dosage could be lowered to 10 mg/day for tolerability reasons. No dosage adjustments were permitted beyond week 4.

Assessments

Patient visits occurred weekly through week 6, then biweekly for the remaining 18 weeks. Assessments included body weight and waist circumference (both measured in triplicate), vital signs, ECG, adverse events, extrapyramidal symptoms (Abnormal Involuntary Movement Scale [AIMS] [28], Simpson-Angus Scale [29], Barnes Akathisia Rating Scale [30]), the Columbia-Suicide Severity Rating Scale (31), the Positive and Negative Syndrome Scale (PANSS) (32), and the Clinical Global Impressions severity scale (CGI-S) (33). Blood samples for fasting (≥8 hours by self-report) metabolic laboratory parameters (triglycerides, cholesterol, glucose, and insulin) and nonfasting hemoglobin A1c were collected.

Primary and Secondary Endpoints

The co–primary endpoints were percent change from baseline at week 24 in body weight and the proportion of patients with ≥10% weight gain from baseline at week 24.

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

The key secondary endpoint was proportion of patients with ≥7% weight gain at week 24. The cutoffs of 10% and 7% were selected on the basis of commonly accepted thresholds of clinically significant changes in weight for weight management and psychiatric treatments, respectively.

Statistical Analysis

The initial target sample size was 200 patients per treatment group. This sample size was estimated to provide ≥90% power to detect significant differences in mean percent change in body weight of 4% (SD 9%) and in the proportion of patients with ≥10% weight gain of 13% at week 24, assuming a cumulative dropout rate of 40%. A prespecified unblinded interim analysis for sample size reestimation was conducted by an independent statistical center when 50% of patients completed the double-blind treatment period or discontinued. Because the conditional power of the co–primary endpoints was less than 90% based on the interim results, the sample size was subsequently increased to 540 patients.

Safety was assessed in patients who received at least one dose of study drug. Weight and antipsychotic efficacy were assessed in all patients who had at least one postbaseline weight assessment.

To control for multiplicity, both co–primary endpoints were tested at an alpha of 0.05 based on the method described by Cui et al. to adjust for the unblinded interim analysis (34). The key secondary endpoint would be tested only if both co–primary endpoints were met.

Missing weight assessments were imputed by multiple imputation sequentially for each visit, using a regression method. The imputation regression model included treatment, race, and baseline age group as factors and body weight at all previous visits (including baseline) as covariates. Five hundred imputations were carried out. The co–primary endpoint of percent change from baseline in body weight at week 24 was analyzed by analysis of covariance (ANCOVA) based on the imputed data sets. The ANCOVA model included treatment, race, and age group as factors and baseline weight as a covariate. Results were combined using Rubin's method. Additional details are provided in the online supplement.

Analysis of the other co–primary endpoint and the key secondary endpoint (proportion of patients with ≥10% and ≥7% weight gain at week 24, respectively) was carried out using a logistic regression model based on the same multiply imputed weight data as the percent change from baseline in body weight at week 24.

Analyses of change from baseline in body weight and waist circumference at each visit were similar to those of the co–primary endpoint of percent change in body weight at week 24. Change from baseline in metabolic laboratory parameters, PANSS score, and CGI-S score were analyzed using a mixed model with repeated measures; the model included treatment, visit, treatment-by-visit interaction, race, and age group as categorical fixed effects and baseline weight as a covariate, with an unstructured covariance structure and Kenward-Roger approximation to adjust the denominator degree of freedom.

RESULTS

Patient Disposition and Baseline Characteristics

Of 561 patients who underwent randomization, 550 (combined olanzapine/samidorphan group, N 274; olanzapine group, N 276) entered double-blind treatment (see Figure S1B in the online supplement). In all, 352 (64%) patients completed treatment, with similar completion rates in the two treatment groups. The most common reasons for discontinuation with combined olanzapine/samidorphan and with olanzapine were adverse events (12.0% and 9.8%, respectively), withdrawal by participant (8.4% and 9.8%), and lost to follow-up (8.0% and 9.4%) (see Figure S1B). Randomization was balanced between groups at baseline for demographic characteristics, including race and BMI (Table 1). Only minimal differences were noted between groups on prior antipsychotic medications used before randomization (see Table S1 in the online supplement).

Drug Exposure

Mean olanzapine dosage, calculated as time-weighted average dosage of olanzapine during the entire study, was similar between groups (combined olanzapine/samidorphan group: 16.8 mg/day, SD 3.94; olanzapine group, 16.9 mg/day, SD 3.57), with most patients (79.6%) taking 20 mg/day as the final dosage.

Concomitant Medications

Overall, patients in the combined olanzapine/samidorphan group and in the olanzapine group had similar concomitant medication use during the treatment period (74.1% [203/274] and 76.4% [211/276], respectively). The most frequently used concomitant medications (≥10% of patients in either treatment group) in the combined olanzapine/samidorphan and olanzapine groups were risperidone (20.1% [55/274] and 20.3% [56/276], respectively), ibuprofen (12.4% [34/274] and 10.9% [30/276]), quetiapine fumarate (10.6% [29/274] and 12.0% [33/276]), and aripiprazole (5.8% [16/274] and 10.5% [29/276]). The concomitant use of non-olanzapine antipsychotics reflects patients tapering off their prior antipsychotic medications during the first 2 weeks.

Weight and Metabolic Effects

Weight effects. For the co–primary endpoint, percent change from baseline in body weight at week 24, the least squares mean percent change was 4.21% (SE 0.681%) for the combined olanzapine/samidorphan group and 6.59% (SE 0.668%) for the olanzapine group. The least squares mean difference between the combined olanzapine/samidorphan group and the olanzapine group was 2.38% (SE 0.765%; p 0.003) (Figure 1A; see also Table S2 in the online supplement). At each visit from week 6 through week 22, the 95% confidence

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

intervals for the between-group difference in percent change in weight did not include zero, consistent with the primary endpoint at week 24 (Figure 1A). Weight gain in the combined olanzapine/samidorphan group stabilized from week 6 onward, whereas weight continued to increase in the olanzapine group over the 24-week treatment period. At week 24, the least squares mean change in body weight was 3.18 kg in the olanzapine/samidorphan group and 5.08 kg in the olanzapine group.

Fewer patients receiving combined olanzapine/samidorphan experienced weight gain across a wide range of thresholds for percent change in body weight compared with olanzapine (Figure 1B,C). The proportion of patients with ≥10% weight gain at week 24 (co–primary endpoint) was significantly lower in the combined olanzapine/samidorphan group (N 47 [17.8%]) than in the olanzapine group (N 81 [29.8%]; number needed to treat [NNT] 7.29); the odds ratio for ≥10% weight gain at week 24 in the combined olanzapine/samidorphan group compared with the olanzapine group was 0.50 (95% CI 0.31, 0.80; p 0.003) (see Table S2 in the online supplement).

For the key secondary endpoint, 27.5% of patients in the combined olanzapine/samidorphan group and 42.7% in the olanzapine group experienced ≥7% weight gain (NNT 6.29) (Figure 1B,C; see also Table S2 in the online supplement). The odds ratio for ≥7% weight gain at week 24 with combined olanzapine/samidorphan compared with olanzapine was 0.50 (95% CI 0.33, 0.76; p 0.001) (see Table S2).

Waist circumference. At week 24, the least squares mean change from baseline in waist circumference was 2.36 cm (SE 0.561) in the combined olanzapine/samidorphan group and 4.47 cm (SE 0.546) in the olanzapine group (least squares mean difference: 2.12 cm [SE 0.628]; 95% CI 3.35, 0.89). Separation in waist circumference occurred early, with smaller increases in waist circumference in the combined olanzapine/samidorphan group compared with the olanzapine group at all visits. Initially at week 1, and then at each visit from week 4 through week 24, the 95% confidence intervals for the between-group difference in waist circumference did not include zero (Figure 2). At week 24, 26.8% of the combined olanzapine/samidorphan group and 43.2% of the olanzapine group had a waist circumference increase of ≥5 cm, a finding associated with increased mortality risk (35); the risk difference was 17.1% (95% CI 26.3, 7.8; odds ratio 0.47; NNT 5.86).

TABLE 1. Baseline characteristics of participants in a study of weight gain with combined olanzapine/samidorphan in schizophrenia[a]

Characteristic	Combined Olanzapine/Samidorphan (N=274)		Olanzapine (N=276)	
	Mean	SD	Mean	SD
Age (years)	40.3	9.79	40.1	10.01
	N	%	N	%
Sex				
Male	193	70.4	207	75.0
Female	81	29.6	69	25.0
Race				
Black or African American	199	72.6	193	69.9
White	63	23.0	65	23.6
Asian	4	1.5	4	1.4
American Indian or Alaska Native	2	0.7	2	0.7
Native Hawaiian or other Pacific Islander	1	0.4	0	0
Other	2	0.7	4	1.4
Multiple[b]	3	1.1	8	2.9
	Mean	SD	Mean	SD
Body weight (kg)	77.17	13.69	77.57	13.47
Body mass index	25.38	3.13	25.52	3.19

[a] Baseline was defined as the last nonmissing observation before the first dose of study drug.
[b] Patients who reported more than one race were counted once under the multiple races category.

Metabolic laboratory parameters. Changes from baseline to week 24 in glycemic and lipid laboratory parameters were generally small and similar for the two treatment groups and tended to occur early (Table 2). The largest changes in any of these parameters were in triglyceride levels, where least squares mean increases of 26.77 mg/dL (SE 5.78) and 29.36 mg/dL (SE 5.69) were observed in the combined olanzapine/samidorphan and olanzapine groups, respectively.

Safety

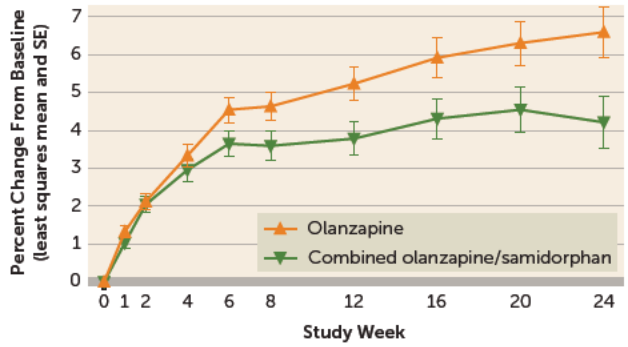
Adverse events were reported in 74.1% and 82.2% of the combined olanzapine/samidorphan and olanzapine groups, respectively. The most commonly reported adverse events (≥10%) in the two groups were weight increase (24.8% and 36.2%, respectively), somnolence (21.2% and 18.1%), dry mouth (12.8% and 8.0%), and increased appetite (10.9% and 12.3%) (Table 3). Most adverse events were mild to moderate in severity. Twelve percent of patients in the combined olanzapine/samidorphan group discontinued treatment because of an adverse event, compared with 9.8% in the olanzapine group (Table 3; see also Figure S1B in the online supplement).

No deaths occurred during the study, and serious adverse events were reported in 3.6% and 2.5% of patients in the combined olanzapine/samidorphan and olanzapine groups, respectively (Table 3). The only serious adverse event occurring in more than one patient was worsening/

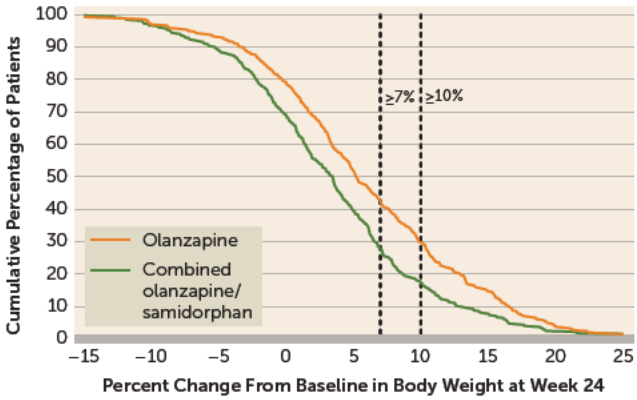
DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

FIGURE 1. Change from baseline in body weight in a study of weight gain with combined olanzapine/samidorphan in schizophrenia[a]

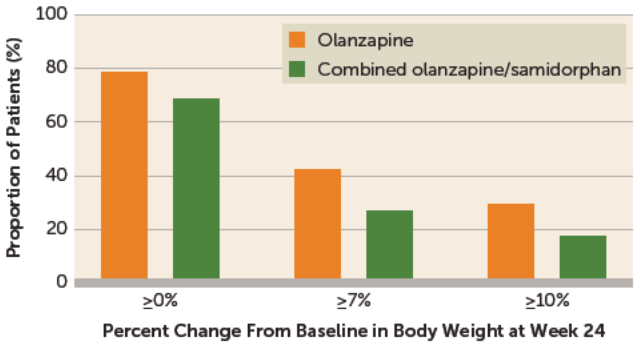
A. Least Squares Mean of Percent Change From Baseline in Body Weight by Visit



B. Cumulative Frequency Distribution of Percent Change From Baseline in Body Weight at Week 24

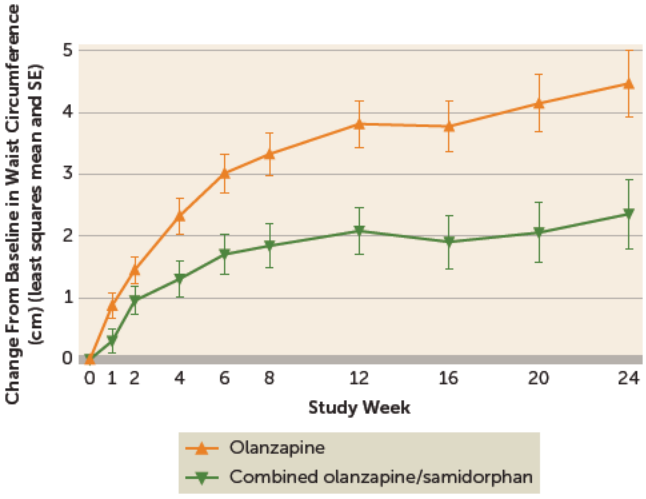


C. Proportion of Patients With Weight Changes at Week 24



[a] Missing postbaseline assessments were imputed based on multiple imputation. Data in panel A were analyzed using an analysis of covariance model with treatment, race (black/African American, nonblack/non African American), and age group (<30 years, ≥30 years) as factors and baseline body weight as the covariate. Baseline was defined as the last nonmissing value before the first dose of study drug.

FIGURE 2. Least squares mean change from baseline in waist circumference by visit in a study of weight gain with combined olanzapine/samidorphan in schizophrenia[a]



[a] Waist circumference analysis was based on an analysis of covariance (ANCOVA) model with a multiple imputation approach for missing postbaseline assessments. The ANCOVA model included treatment, race (black/African American, nonblack/non African American), and age group (<30 years, ≥30 years) as factors and baseline body weight as the covariate. Baseline was defined as the last nonmissing value before the first dose of study drug.

exacerbation of schizophrenia symptoms (one patient [0.4%] in the combined olanzapine/samidorphan group and three patients [1.1%] in the olanzapine group).

There were no clinically meaningful changes or differences observed in vital signs, ECG results, movement disorder scale scores (AIMS, Simpson-Angus Scale, or Barnes Akathisia Rating Scale), or Columbia-Suicide Severity Rating Scale scores for patients in the two treatment groups.

The overall safety profile of combined olanzapine/samidorphan in this 24-week study was consistent with that of olanzapine, except for fewer adverse events of weight increase in the combined olanzapine/samidorphan group.

Antipsychotic Efficacy

PANSS and CGI-S scores. The mean PANSS total score at baseline was 68.2 (SD 9.51) in the combined olanzapine/samidorphan group and 70.2 (SD 9.47) in the olanzapine group. The PANSS total score improved similarly in both groups; the least squares mean change from baseline to week 24 was 8.2 (SE 0.73) in the combined olanzapine/samidorphan group and 9.4 (SE 0.72) in the olanzapine group. The least squares mean difference between treatments was 1.2 (95% CI 0.9, 3.2). Reductions in CGI-S score from baseline to week 24 were similar between the two treatment groups, consistent with the changes in PANSS total score (see Figure S4 in the online supplement).

DISCUSSION

In this 24-week study in patients with schizophrenia, treatment with combined olanzapine/samidorphan resulted in significantly less weight gain compared with olanzapine monotherapy. Differences in weight gain were apparent at week 6 and remained lower in the combined olanzapine/samidorphan group at each subsequent visit through week 24. The weight distribution profile in the combined

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

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.