Dapsone Gel 5% in Combination With Adapalene Gel 0.1%, Benzoyl Peroxide Gel 4% or Moisturizer for the Treatment of Acne Vulgaris: A 12-Week, Randomized, Double-Blind Study

Alan B. Fleischer Jr. MD,[a] Alan Shalita MD,[b] Lawrence F. Eichenfield MD,[c,d] William Abramovits MD,[e] Anne Lucky MD,[f] Steven Garrett DDS,[g] for the Dapsone Gel in Combination Treatment Study Group*

[a]Wake Forest University School of Medicine Medical Center, Winston-Salem, NC
[b]SUNY Downstate Medical Center, Brooklyn, NY
[c]Rady Children's Hospital and Health Center, San Diego, CA
[d]University of California, San Diego, CA
[e]Dermatology Treatment & Research Center, Dallas, TX
[f]Dermatology Research Associates, Inc., Cincinnati, OH
[g]QLT USA, Inc., Fort Collins, CO
*Additional members of the Dapsone Gel in Combination Treatment Study Group are listed in the Disclosures.

ABSTRACT

Purpose: To evaluate the safety and efficacy of dapsone gel 5% in the treatment of acne when used in combination with adapalene gel 0.1%, benzoyl peroxide gel 4% or moisturizer.

Methods: This was a twelve-week, randomized, double-blind study. Patients aged 12 years and older (n=301) applied dapsone gel twice daily and were randomly assigned (1:1:1) to one of three additional treatments, applied once daily.

Results: By week 12, dapsone gel combined with any of the three additional treatments reduced the mean number of inflammatory lesions. However, the authors did not detect a significant difference in the reduction of inflammatory lesions when dapsone was used in combination with adapalene gel or with benzoyl peroxide gel compared to the dapsone plus moisturizer combination group (P=0.052 for both versus moisturizer combination). Patients treated with dapsone gel combined with adapalene showed a significantly better response in reduction in non-inflammatory and total acne lesion count than those who received the moisturizer combination. Local adverse reactions in all three treatment groups were minimal and generally mild in severity.

Conclusion: Dapsone gel in combination with adapalene gel or benzoyl peroxide gel is safe and well tolerated for the treatment of acne vulgaris.

INTRODUCTION

Acne vulgaris is a complex skin disorder involving multiple abnormalities of the pilosebaceous unit, including hyperkeratinization, seburn production, bacterial proliferation and inflammation.[1] Disease onset occurs commonly during adolescence and is characterized by papules, pustules and comedones. The prevalence of acne is close to 100% of the population, with individuals differing only in severity of expression.[2] Most anti-acne medications do not act against all four of the pathophysiologic features of acne, so combination therapy is often used in the management of all but the most severe forms of acne.[3-5]

Dapsone is a sulfone with anti-inflammatory properties. Its anti-inflammatory properties include inhibition of neutrophil myeloperoxidase and eosinophil peroxidase and suppression of hypochlorous acid production.[6] Dapsone scavenges reactive oxygen species and minimizes associated inflammation,[7] suppresses neutrophil recruitment and local production of toxic respiratory and secretory products, and inhibits chemoattractant-induced signal transduction.[8] A number of inflammatory as well as bullous diseases respond, in varying degrees, to oral dapsone, including acne vulgaris.[9-11] High doses of oral dapsone have been associated with systemic toxicity and dose-related hematological adverse events, so its use is generally reserved for the most severe forms of these skin diseases and when patients can be monitored closely.[9,12]

Advances in cutaneous pharmacology have led to the development of a topical gel formulation of dapsone, dapsone gel 5% (Aczone®; Allergan, Inc., Irvine, CA). It allows clinically effective doses of dapsone to be administered topically with minimal systemic absorption.[13] In two double-blind, randomized, 12-week, vehicle-controlled studies,[14] significantly better outcomes were observed for patients applying dapsone gel versus the vehicle. The safety profile, including adverse events, laboratory studies, and local signs and symptoms such as oiliness, dryness and erythema demonstrated virtually no difference between dapsone gel-treated and vehicle-treated

patients. Similar results were observed in an open-label safety study conducted over one year.[15]

This report assessed the safety and efficacy of dapsone gel when coadministered with one of the following: adapalene gel 0.1% (adapalene gel), benzoyl peroxide gel 4% (benzoyl peroxide gel) or moisturizer. Levels of dapsone exposure were also assessed. Adapalene gel was selected because it has consistently demonstrated a more favorable tolerance profile than other topical retinoids,[16] and benzoyl peroxide gel was chosen because it is often used in combination with other acne treatments.[5]

METHODS

Study Design

A three-arm, 12-week, randomized, double-blind study was conducted to evaluate the safety and efficacy of dapsone gel in combination with adapalene gel, benzoyl peroxide gel or moisturizer in the treatment of acne vulgaris. A total of 22 centers in the United States (U.S.) participated in the study between February 2005 and July 2005.

All eligible patients applied dapsone gel and were also randomly assigned in a 1:1:1 ratio, according to a computer-generated randomization table, to one of three additional treatment groups: adapalene gel, benzoyl peroxide gel or moisturizer (chosen as a nonactive control). The investigators, patients and sponsor personnel were blinded to the treatment assignment. To maintain blinding, personnel who were not involved in efficacy or safety assessments conducted the drug accountability and test-article-weight assessments.

Patients applied a thin film of dapsone gel twice daily to the entire face after washing with a standard, noncomedogenic, soap-free cleanser (Cetaphil® Cleanser; Galderma Laboratories, L.P., Ft. Worth, TX): once in the morning and again at least one hour before bedtime. Ten minutes after the evening application of dapsone gel, patients applied a thin layer of adapalene gel (Differin® Gel, 0.1%; Galderma S.A.), benzoyl peroxide gel (Brevoxyl®-4 Gel, Stiefel Laboratories, Inc.) or moisturizer (Cetaphil® Daily Facial Moisturizer SPF 15; Galderma Laboratories, L.P.), and gently rubbed it in until it completely disappeared. Patients were instructed to maintain their current skin care regimen throughout the study: moisturizers, sunscreens and cosmetics could be used one hour after study treatment applications, but use of new cosmetics, cleansers or medicated makeup was prohibited. Participants could also treat acne-affected areas other than the face, including chest and back; however, these areas were not assessed for efficacy.

These studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with the Goed Clinical Practice Guidelines. The protocols for each study center were reviewed and approved by an institutional review board. Written informed assent and consent was obtained from each patient or his/her parent or guardian, as appropriate, before the start of study procedures. If a patient did not understand English, a validated, translated informed consent agreement was provided.

Patients

Male and female patients 12 years of age or older with a clinical diagnosis of acne vulgaris involving the face were enrolled in these studies. Patients were to have a Global Acne Assessment Score (GAAS) of at least 2 at baseline, and a minimum of 20 inflammatory lesions (defined to include papules and pustules) and 20 noninflammatory lesions (comedones) above the mandibular line at baseline. Individuals with severe cystic acne, acne conglobata, or any active or developing nodules above the mandibular line at baseline were excluded from participation. Other exclusion crite-

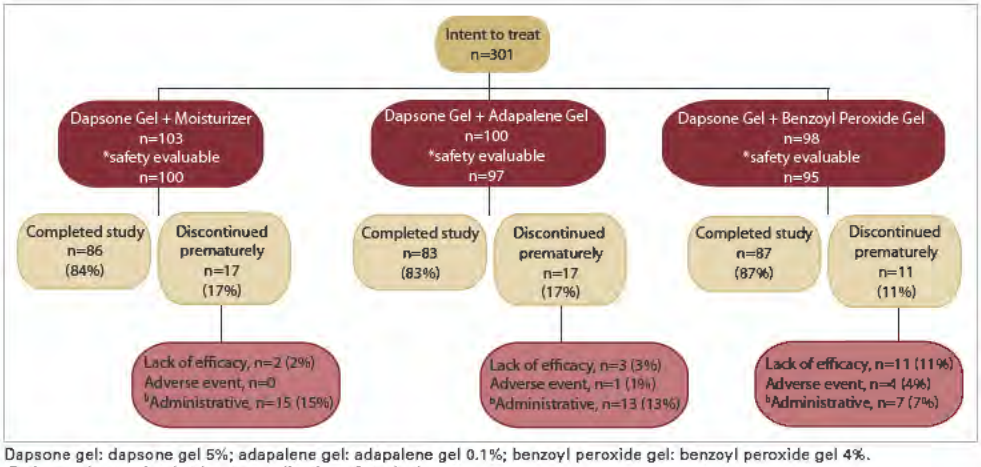

FIGURE 1. Flow chart of patient disposition.

Dapsone gel: dapsone gel 5%; adapalene gel: adapalene gel 0.1%; benzoyl peroxide gel: benzoyl peroxide gel 4%.
[a]Patients who received at least 1 application of study drug.
[b]Includes loss to follow-up, voluntary withdrawal, protocol violation, treatment, noncompliance, and other reasons not specified.

ria included use within two weeks of baseline of topical drugs or treatments that could affect acne, including retinoids, antibiotics and anti-inflammatory agents; use within four weeks of baseline of systemic immunosuppressive drugs or systemic medications or therapy known to affect acne or inflammatory responses; use of isotretinoin within three months of baseline; or known allergy or hypersensitivity to dapsone, adapalene, benzoyl peroxide or any component of the study treatments. Women of childbearing potential could not be pregnant or nursing, had to be practicing an effective method of birth control as determined by the enrolling physician, and, if using hormonal contraception, had to have been using a stable dose for a minimum of three months. Systemic contraceptives were not to be initiated during the study.

Efficacy and Safety Assessments

All patients underwent a dermatologic examination at screening/baseline and weeks 2, 4, 8 and 12. At each of these visits, investigators recorded the patient's GAAS and counted the number of inflammatory and non-inflammatory acne lesions present.

The primary efficacy endpoint was the mean percentage reduction from baseline in inflammatory acne lesion counts at week 12 (or end of treatment). Secondary efficacy endpoints included mean percentage reduction from baseline for non-inflammatory and total lesion counts; incidence of success based on the GAAS; and mean reduction from baseline in lesion counts for inflammatory, non-inflammatory and total acne lesions. Incidence of success based on the 5-point GAAS scale was defined as a rating of zero ("none" or no evidence of facial acne vulgaris) or 1 ("minimal," where a few non-inflammatory lesions are present and a few inflammatory lesions may be present). The total lesion count was the sum of both inflammatory and non-inflammatory lesions.

Adverse events and local signs and symptoms (adverse reactions of facial oiliness, peeling, dryness and erythema) were monitored throughout the study. Physical examinations that included vital signs, height and weight were conducted at baseline and week 12 (or end of treatment). Patients were specifically queried at each study visit, including at baseline, for the presence of local signs or symptoms; a worsening of these symptoms from baseline or the appearance of any other local sign or symptom was reported as an application-site adverse event. Blood was drawn for the determination of plasma dapsone and N-acetyl plasma dapsone levels at baseline, week 2 and week 12. Plasma dapsone analyses were performed at a central laboratory (MDS Pharma Services; Saint-Laurent, Quebec, Canada).

Statistical Methods

Efficacy results are presented for the intent-to-treat (ITT) population (defined as all enrolled patients to whom study drug was dispensed) and were summarized for each treatment group at weeks 2, 4, 8 and 12. Missing values for the ITT data set were analyzed with a last-observation-carried forward method. Safety results use the safety-evaluable population (all patients who received at least one dose of study drug or reported an adverse event) and were also summarized at these time points.

FIGURE 2. Mean percentage reduction in lesion counts. **a)** Inflammatory lesions (primary endpoint): Dapsone gel + moisturizer versus dapsone gel + adapalene or dapsone gel + BP, both P=0.052 at week 12. **b)** Non-inflammatory lesions: Dapsone gel + moisturizer versus dapsone gel + adapalene or dapsone gel + BP, P<0.001 and P=0.086, respectively, at week 12. **c)** Total lesions: Dapsone gel + moisturizer versus dapsone gel + adapalene or dapsone gel + BP, P=0.004 and P=0.056, respectively, at week 12. Wilcoxon/Mann Whitney test; BP=benzoyl peroxide gel 4%; adapalene=adapalene gel 0.1%.

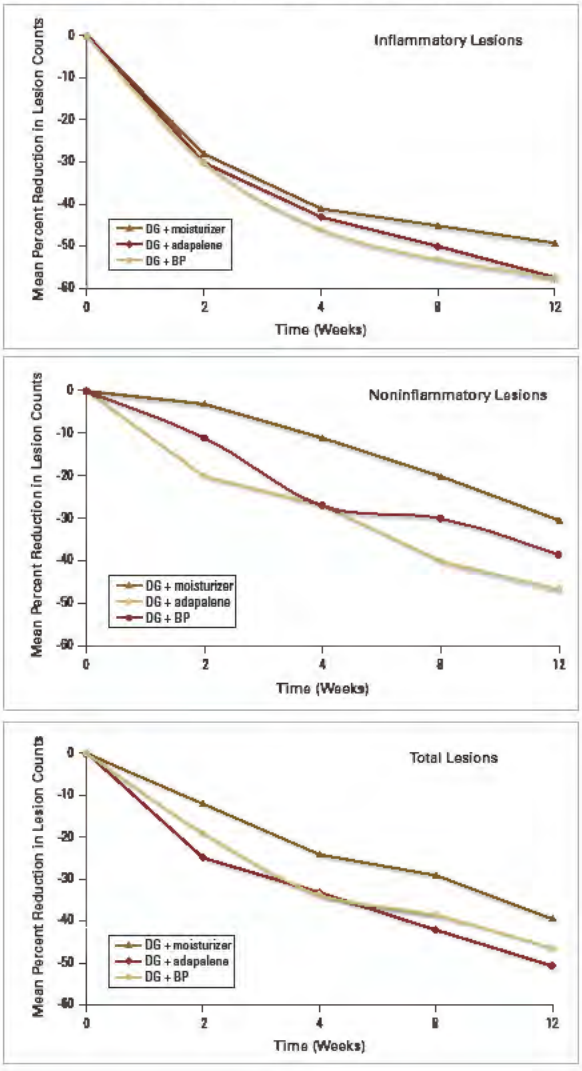

TABLE 1.

Patient Demographics and Baseline Characteristics

	Dapsone Gel + Moisturizer (n=103)	Dapsone Gel + Adapalene Gel (n=100)	Dapsone Gel + Benzoyl Peroxide Gel (n=98)
Sex, n (%)			
Male	52 (50)	48 (48)	47 (48)
Female	51 (50)	52 (52)	51 (52)
Race/Ethnicity, n (%)			
White	61 (59)	63 (63)	56 (57)
Black	15 (15)	15 (15)	21 (21)
Hispanic	20 (19)	16 (16)	16 (16)
Asian	4 (4)	2 (2)	2 (2)
Other	3 (3)	4 (4)	3 (3)
Mean Age, y (Range)	18 (12-38)	20 (12-44)	18 (12-44)
Acne lesion Counts at Baseline, mean [±SD]			
Inflammatory	33 [±13]	32 [±15]	31 [±11]
Non-inflammatory	52 [±32]	50 [±36]	34 [±41]
Total[a]	85 [±35]	81 [±43]	80 [±37]
GAAS[b] at Baseline, n (%)			
Mild	16 (16)	14 (14)	11 (11)
Moderate	83 (81)	81 (81)	82 (84)
Severe	4 (4)	5 (5)	5 (5)

Dapsone gel: dapsone gel 5%; adapalene gel: adapalene gel 0.1%; benzoyl peroxide gel: benzoyl peroxide gel 4%.
[a] Total lesions = inflammatory + non-inflammatory lesions.
[b] Global Acne Assessment Score, where 2 = mild, 3 = moderate, 4 = severe. No patient had a score of 0 (no acne) or 1 (minimal) at baseline.

TABLE 2.

Mean Percentage Reduction in Lesion Counts by Week 12

	Dapsone Gel + Moisturizer (n=103)	Dapsone Gel + Adapalene Gel (n=100)	Dapsone Gel + Benzoyl Peroxide Gel (n=98)
Inflammatory Lesions			
Mean % reduction in acne lesion counts [±SD]			
Week 2	26 [± 28]	30 [± 29]	31 [± 35]
Week 4	42 [± 32]	43 [± 29]	47 [± 30]
Week 8	47 [± 33]	51 [± 31]	54 [± 38]
Week 12[a]	49 [± 35]	57 [± 36]	58 [± 36]
***P* Values[b]**			
DG + moisturizer versus DG + adapalene gel[a]			0.052
DG + moisturizer versus DG + BP gel[a]			0.052
DG + adapalene gel versus DG + BP gel[c]			0.893
Non-inflammatory lesions			
Mean % reduction in acne lesion counts [±SD]			
Week 2	3 [± 36]	21 [± 28]	12 [± 33]
Week 4	11 [± 36]	26 [± 36]	26 [± 34]
Week 8	21 [± 35]	40 [± 31]	31 [± 45]
Week 12[a]	30 [± 38]	47 [± 38]	38 [± 43]
***P* Values[b]**			
DG + moisturizer versus DG + adapalene gel			<0.001
DG + moisturizer versus DG + BP gel			0.087
DG + adapalene gel versus DG + BP gel			0.210
Total Lesions			
Mean % reduction in acne lesion counts [±SD]			
Week 2	13 [± 26]	24 [± 24]	19 [± 27]
Week 4	24 [± 28]	33 [± 28]	34 [± 28]
Week 8	31 [± 28]	44 [± 26]	40 [± 39]
Week 12[a]	39 [± 29]	51 [± 31]	46 [± 36]
***P* Values[b]**			
DG + moisturizer versus DG + adapalene gel			0.004
DG + moisturizer versus DG + BP gel			0.056
DG + adapalene gel versus DG + BP gel			0.620

DG: dapsone gel 5%; adapalene gel: adapalene gel 0.1%; BP gel: benzoyl peroxide gel, 4%.
[a] Primary analysis.
[b] Wilcoxon/Mann Whitney test. $P \leq 0.05$ was considered significant.
[c] Secondary analysis.

The primary efficacy endpoint was the mean percentage reduction from baseline in inflammatory lesion counts at week 12 (ITT population). The planned sample size of 300 evaluable patients (100 per treatment arm) was based on the expected difference between the dapsone gel + moisturizer group and the other treatment groups for the primary endpoint. A 40% response for the dapsone gel + moisturizer group and a 45% response for the other dapsone gel combination-treatment groups, with a common standard deviation of 10, would provide adequate (≥ 80%) power to detect a difference between the treatment groups. A test for normality using the Kolmogorov-Smirnov statistic was performed. Because this test was significant at $P \leq 0.05$, a Wilcoxon/Mann-Whitney test was used to analyze the percentage reduction in inflammatory lesion counts.

The secondary endpoints of mean percentage reduction in non-inflammatory and total lesion counts, mean reduction in acne lesion counts from baseline (all three categories), and acne lesion counts (all three categories) were analyzed in the same way as the primary endpoint. Most study centers randomized fewer than 15 study subjects, so the effect of centers was considered negligible; therefore, the incidence of success based on a GAAS score of 0 (none) or 1 (minimal) at week 12 was compared using pair-wise chi-square tests.

Adverse events, regardless of relationship to study medication, were tabulated and summarized by incidence as application-site or non–application-site events, using the safety-evaluable data set. The local adverse reaction assessments were summarized using frequencies and percentages by treatment group for each time point. Relationship to treatment was determined by the investigator.

TABLE 3.

Adverse Events Occurring in at Least 2% of Patients in Any Treatment Group (Safety-Evaluable Population)

	No. (%) of Patients		
	Dapsone Gel + Moisturizer (n=100)	Dapsone Gel + Adapalene Gel (n=97)	Dapsone Gel + Benzoyl Peroxide Gel (n=95)
All Adverse Events[a]			
Any event	31 (31)	41 (42)	29 (31)
Nasopharyngitis	5 (5)	4 (4)	4 (4)
Upper respiratory tract infection	4 (4)	3 (3)	2 (2)
Headache	2 (2)	2 (2)	2 (2)
Pharyngitis	2 (2)	1 (1)	3 (3)
Nasal congestion	3 (3)	1 (1)	1 (1)
Cough	2 (2)	2 (2)	0
Sinusitis	1 (1)	2 (2)	0
Abrasion	2 (2)	1 (1)	0
Ear pain	0	0	2 (2)
Vaginosis fungal	0	2 (2)	0
Treatment-Related Adverse Events[b]			
Any treatment-related event	4 (4)	17 (18)	9 (10)
Burning	1 (1)	10 (10)[c]	1 (1)
Drug interaction	0	0	7 (7)[d]
Pruritus	1 (1)	4 (4)	1 (1)
Rash	2 (2)	0	0

Dapsone gel: dapsone gel 5%; adapalene gel: adapalene gel 0.1%; benzoyl peroxide gel: benzoyl peroxide gel 4%.
[a] Regardless of relationship to treatment.
[b] Investigators determined relationship to treatment.
[c] Consistent with the 10% to 40% incidence described in the adapalene gel 0.1% package insert.
[d] All drug interactions in the dapsone gel + benzoyl peroxide group were application-site adverse events involving a temporary tan residue at the application site.

TABLE 4.

Patients Who Experienced Treatment-Related Local Signs and Symptoms Which Were Moderate-to-Severe in Intensity (Safety-Evaluable Population)

	No. (%) of Patients					
	Dapsone Gel + Moisturizer (n=100)		Dapsone Gel + Adapalene Gel (n=97)		Dapsone Gel + Benzoyl Peroxide Gel (n=95)	
	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12
Oiliness	25 (25)	6 (6)	21 (22)	5 (5)	13 (14)	4 (4)
Erythema	19 (19)	8 (8)	16 (17)	3 (3)	15 (16)	4 (4)
Dryness	2 (2)	0	0	1 (1)	3 (3)	1 (1)
Peeling	0	0	0	0	0	2 (2)
Rash	2 (2)		0		0	

TABLE 5.

Plasma Dapsone and N-Acetyl Dapsone Concentrations (ng/mL) by Treatment Group and Study Visit

	Treatment Group		
	Dapsone Gel + Moisturizer	Dapsone Gel + Adapalene Gel	Dapsone Gel + Benzoyl Peroxide Gel
Plasma Dapsone Concentrations			
Baseline			
Mean ± SD	0.051 ± 0.015	0.052 ± 0.028	0.049 ± 0.000
Week 2			
Mean ± SD	6.37 ± 5.71	9.50 ± 9.87	11.13 ± 9.90
Week 12			
Mean ± SD	4.75 ± 5.97	7.10 ± 8.95	6.72 ± 7.68
Plasma N-acetyl Dapsone Concentrations			
Baseline			
Mean ± SD	0.049 ± 0.00	0.049 ± 0.00	0.049 ± 0.00
Week 2			
Mean ± SD	3.09 ± 3.23	4.00 ± 5.24	4.13 ±4.67
Week 12			
Mean ± SD	2.34 ± 3.07	2.73 ± 4.63	2.35 ± 2.53

Values below the limit of detection (0.05 ng/mL) were set to 0.049 ng/mL for both plasma measurements.

Baseline patient demographics and lesion characteristics, vital signs, and plasma levels of dapsone and N-acetyl dapsone were summarized using descriptive statistics (mean, standard deviation, median, minimum and maximum for quantitative variables, and numbers and percentages for categorical variables).

RESULTS

Patient Disposition and Baseline Characteristics

A total of 301 patients were enrolled in the study and received the study drug; this group composed the ITT population (Figure 1). The safety-evaluable population, defined as all enrolled subjects who applied the study drug or reported an adverse event, included 292 patients. There were minor differences in patients who discontinued the study, with 11% of patients in the dapsone gel + benzoyl peroxide group discontinuing versus approximately 17% in the dapsone gel + adapalene or dapsone gel + moisturizer groups. Most premature study discontinuations were for administrative reasons, including loss to follow-up, voluntary withdrawal, protocol violation and treatment noncompliance (Figure 1). Nine subjects discontinued the study due to 16 adverse events (application-site and non–application-site) and/or local adverse reactions (see Safety Results).

Patients in the dapsone gel + moisturizer and dapsone gel + adapalene gel groups were treated for a mean of 76.2 days,

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.