



# A Pharmacokinetic and Pharmacodynamic Drug Interaction Study of Acamprosate and Naltrexone

Barbara J. Mason, Ph.D., Anita M. Goodman, M.D., Russell M. Dixon, M.D.,  
Magdy H. Abdel Hameed, Ph.D., Thierry Hulot, Pharm.D., Keith Wesnes, Ph.D.,  
John A. Hunter, M.S., and Michael G. Boyeson, Ph.D.

*Acamprosate and naltrexone have each demonstrated safety and efficacy for alcohol dependence in placebo-controlled clinical trials. There is scientific and clinical interest in evaluating these drugs in combination, given their high tolerability, moderate effect sizes, different pharmacological profiles and potentially different effects on drinking outcomes. Thus, this is the first human pharmacokinetic and pharmacodynamic drug interaction study of acamprosate and naltrexone. Twenty-four normal, healthy adult volunteers participated in a double-blind, multiple dose, within subjects, randomized, 3-way crossover drug interaction study of the standard therapeutic dose of acamprosate (2 g/d) and the standard therapeutic dose of naltrexone (50 mg/d), given alone and in combination, with seven days per treatment condition and seven days washout between treatments. Blood samples were collected on a standardized schedule for pharmacokinetic analysis of*

*naltrexone, 6- $\beta$ -naltrexol, and acamprosate. A computerized assessment system evaluated potential drug effects on cognitive functioning. Coadministration of acamprosate with naltrexone significantly increased the rate and extent of absorption of acamprosate, as indicated by an average 33% increase in acamprosate maximum plasma concentration, 33% reduction in time to maximum plasma concentration, and 25% increase in area under the plasma concentration-time curve. Acamprosate did not affect the pharmacokinetic parameters of naltrexone or 6- $\beta$ -naltrexol. A complete absence of negative interactions on measures of safety and cognitive function supports the absence of a contraindication to co-administration of acamprosate and naltrexone in clinical practice.*

*[Neuropsychopharmacology 27:596–606, 2002]*

© 2002 American College of Neuropsychopharmacology.  
Published by Elsevier Science Inc.

KEY WORDS: *Pharmacodynamics; Pharmacokinetics; Alcohol; Naltrexone; Acamprosate; Cognition*

From the Division of Substance Abuse, Department of Psychiatry and Behavioral Sciences, University of Miami School of Medicine, Miami, FL (BJM), Lipha Pharmaceuticals, Inc., New York, NY (AMG), Covance Clinical Research Unit, Madison, WI (RMD, MHAH, MGB, JAH), Lipha s.a., Lyon, France (TH), and Cognitive Drug Research Limited, Reading, UK (KW).

Address correspondence to: Barbara Mason, Alcohol Disorders Research Unit, 1400 N.W. 10th Avenue, Suite 307A, Miami, FL 33136. Tel.: (305) 243-4059; E-mail: bjmason246@aol.com

Received February 12, 2002; revised April 18, 2002; accepted April 22, 2002.

Online publication: 5/7/02 at [www.acnp.org/citations/Npp050702298](http://www.acnp.org/citations/Npp050702298).

Recent efforts to develop pharmacological interventions for relapse-prevention in newly abstinent alcoholics initially focused on acamprosate (Campral<sup>®</sup>, Aotal<sup>®</sup>) in Europe and naltrexone (ReVia<sup>®</sup>) in the United States of America. Acamprosate and naltrexone have each demonstrated efficacy and safety in randomized, double-blind, placebo-controlled trials in alcohol-dependent outpatient volunteers (Garbutt et al. 1999; Litten and Allen 1998; Mason 2001; Mason and Ownby 2000; Swift 1999). Neither medication interacts with alcohol or has abuse potential or rebound effects when discontinued. Despite these similarities, acamprosate and naltrexone induce their action via very different mecha-

nisms and may affect different behavioral aspects of alcohol dependence.

Acamprosate is a centrally acting synthetic analog of the naturally occurring amino acid neuromediator taurine (Dahchour and de Witte 2000). Chronic alcohol exposure is associated with decreased GABAergic transmission and increased glutamate activity (Grant et al. 1990; Hoffman and Tabakoff 1994). Although the precise mechanism of action or cellular target of acamprosate is not fully elucidated, acamprosate appears to modulate *N*-methyl-*D*-aspartate (NMDA) receptor activity in the glutamate system, and to inhibit the upregulation of voltage-gated  $Ca^{2+}$  channels that is induced by chronic alcohol ingestion and states of withdrawal (Allgaier et al. 2000; Popp and Lovinger 2000). Thus, acamprosate may act on neurobiological mechanisms that may persist for many months following alcohol withdrawal, and that may contribute to the vulnerability for drinking relapse (Borg 1988).

The clinical safety and efficacy of acamprosate was evaluated in 16 placebo-controlled, double-blind trials of 3, 6, or 12 months duration conducted across 11 European countries and involving more than 4,500 male and female outpatients with alcohol dependence (Barrias et al. 1997; Besson et al. 1998; Chick et al. 2000a; Geerlings et al. 1997; Gual and Leher 2001; Ladewig et al. 1993; Lhuintre et al. 1985, 1990; Paille et al. 1995; Pelc et al. 1992, 1997; Poldrugo 1997; Rousseaux et al. 1996; Sass et al. 1996; Tempesta et al. 2000; Whitworth et al. 1996). Fourteen of 16 trials showed a significant advantage for acamprosate over placebo on abstinence measures. There are no serious or rate-limiting adverse effects associated with acamprosate. Mild and transient diarrhea is the only drug-related adverse event that differed consistently from placebo across studies. Acamprosate is not metabolized. It is eliminated by the kidneys and is contra-indicated in cases of renal insufficiency (Saivin et al. 1998). Oral acamprosate tablets are available by prescription in 39 countries, with about 1.5 million people treated with acamprosate worldwide. The Food and Drug Administration granted Investigational New Drug status for acamprosate, and a 21-site, 6-month, double-blind placebo-controlled dose-ranging trial has recently been completed in 601 alcohol-dependent outpatients in support of USA regulatory approval (for methodology see Mason and Ownby 2000).

Naltrexone is a highly selective opioid antagonist (Chang et al. 1979). A large body of pre-clinical studies suggests that endogenous opioids play a role in the reinforcing effects of alcohol, and that blockade of these receptors with an antagonist decreases the positive reinforcing effects of alcohol and reduces drinking (Koob et al. 1998). These findings suggest that an opioid antagonist may not initially prevent sampling of alcohol (i.e., promote abstinence), but may reduce risk of relapse to

excessive drinking in subjects who sample alcohol while taking an opioid antagonist. Double-blind placebo-controlled clinical trials with naltrexone and a structural analog, nalmefene, provide support for the use of opioid antagonists for reducing relapse severity in persons with alcohol dependence (Anton et al. 1999; Mason et al. 1999; O'Malley et al. 1992; Oslin et al. 1997; Volpicelli et al. 1992, 1997), although some recent trials have been inconclusive (Chick et al. 2000b; Kranzler et al. 2000; Krystal et al. 2001). A multicenter safety study found naltrexone to be well tolerated with patients complaining primarily of headache and nausea that tended to be transient in nature (Croop et al. 1997). Naltrexone is metabolized by the hepatic cytosolic enzyme system to form 6- $\beta$ -naltrexol, a major pharmacologically active metabolite (Porter et al. 2000). It is contra-indicated in cases of hepatic insufficiency (Sifton 1997).

With drugs for a common indication where the overall effect size is moderate and there are not overlapping toxicities, it is of interest to explore whether or not coadministration may enhance clinical outcome. There is considerable interest in evaluating the safety of combined administration of acamprosate and naltrexone given the high tolerability of each drug, their different pharmacological profiles (glutamate vs. opiate), potentially different effects on drinking outcomes (e.g., increased abstinence duration vs. decreased relapse severity), and the increasing world-wide availability of both compounds. The objectives of this study are to determine if there is a pharmacokinetic (PK) or pharmacodynamic (PD) drug interaction between acamprosate and naltrexone in normal, healthy adult subjects. Chronic heavy alcohol intake and some pharmacological agents selective for either opioid or NMDA receptors have been associated with changes in memory and cognition (Chaves et al. 1988; Cohen et al. 1983; Kathmann et al. 1996; Malenka 1991; O'Mahony and Doherty 1996; Parsons and Farr 1981; Schneider et al. 1999; Willetts et al. 1990). Therefore, evaluation of a pharmacodynamic drug interaction will focus on tests of cognitive functioning.

## METHODS

### Subjects

Subjects were normal, healthy male and female paid volunteers. The study was conducted under appropriate guidelines for the protection of human subjects, in accordance with the Declaration of Helsinki. To be eligible, subjects had to be 18 to 40 years of age; weigh at least 110 pounds and be within 15% of their normal body weight for height; have negative results on hepatitis panel, HIV antibody, urine drug and alcohol, and pregnancy (if female) tests; and provide written in-

formed consent. Subjects were excluded if they met current Diagnostic and Statistical Manual Fourth Edition (American Psychiatric Association 1994) criteria for alcohol or other drug use disorders, including nicotine and opiates; had clinically relevant medical or psychiatric disorders; used any prescribed medications within two weeks prior to study entry, except contraceptives; used over-the-counter preparations within one week prior to study entry, except vitamins which could be continued at the same dosage; used any alcohol, caffeine or xanthine-containing products within 72 h prior to the first dose of study drug for each treatment period; were pregnant, lactating, or refused to use a reliable method of contraception.

### Study Procedures

This was a double-blind, multiple-dose, within subjects, randomized 3-way crossover interaction study of the standard therapeutic doses of acamprosate (2 g/d) and naltrexone (50 mg/d), given alone and in combination. All subjects received all three treatment conditions in an order determined by a computer-generated randomization code. Subjects were admitted to the inpatient clinical research unit on the day prior to the first dose administration and were discharged after completion of study procedures on Day 11, for each treatment condition. Steady state levels of acamprosate are achieved by the seventh day of dosing (Wilde and Wagstaff 1997). Therefore, in order to adequately test for drug interactions, all subjects were dosed with each study medication for seven days and completed PK and PD studies through Day 11 (Hansten and Horn 1993). The 7-day treatment periods were separated with at least a 7-day washout period to avoid carryover drug effects from the previous treatment condition.

### Treatment Conditions

Treatment conditions were: (1) acamprosate 1000-mg (two 500-mg tablets manufactured by Groupe Lipla) administered orally every 12 h, starting at 7:00 A.M., for a total of 13 doses, plus one naltrexone placebo capsule administered orally once daily at 7:00 A.M., for a total of seven doses; (2) two acamprosate placebo tablets administered orally every 12 h starting at 7:00 A.M., for a total of 13 doses, plus one 50-mg naltrexone tablet (one 50-mg ReVia<sup>®</sup> tablet manufactured by DuPont Pharma, over-encapsulated to match naltrexone placebo) administered orally once daily at 7:00 A.M. for a total of seven doses; and (3) acamprosate 1000 mg (two 500-mg tablets) administered orally every 12 h starting at 7:00 A.M., for a total of 13 doses, plus a 50-mg naltrexone tablet administered orally every 24 h starting at 7:00 A.M., for a total of seven doses. A mouth check was performed by Unit staff to verify that the dose was

swallowed. All doses were taken with 240 mL of water thirty minutes prior to consumption of standardized meals, except for Day 7 (PK day) when subjects fasted for 4.5 h post dose. On Day 7, subjects also remained ambulatory, i.e., standing or seated, for 4 h post dose. Use of concomitant medication during the study was prohibited unless pre-approved or necessary in a medical emergency. Any such use and the reason was documented.

### Safety and Tolerability

Clinical laboratory evaluations (hematology, clinical chemistry (fasting), and urinalysis) were performed at screening and during each treatment period at check-in, on Day 2 (24 h after first dose of study drug), on Day 8 (24 h after last dose of study drug), and on Day 11 (prior to each clinic discharge). A serum ( $\beta$ -HCG) pregnancy test was performed for females at screening, at each check-in day, and at study completion (Day 11 of Period 3). A urine screen for drugs of abuse (including alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiates, phencyclidine and propoxyphene) was performed at screening and repeated at each check-in. Complete physical and neurological examinations were performed at screening, with follow-up exams at check-in and Days 7, 8, and 11 of each treatment period. A 12-lead ECG was obtained at screening, check-in of Period 1, and at study completion (Day 11 of Period 3). Vital signs were obtained at screening, at check-in, on Days 1 through 10, prior to and 3 and 6 h following the morning dose, and prior to inpatient discharge on Day 11. In conjunction with vital sign measurement at pre-dose on Days 1 through 10 and on Day 11, subjects were asked "Have there been any changes in the way you feel since the last time you were asked?"

Adverse events were recorded using the Coding Symbols for Thesaurus of Adverse Reaction Terms (Department of Health and Human Services 1995) terminology from check-in through study completion. All adverse events, whether spontaneously reported by the subject or observed by study personnel, were documented along with any medical intervention, and evaluated according to standardized criteria in terms of severity, frequency, duration and causal relationship to study medication.

### Pharmacokinetic Parameters

Acamprosate has no biologically active metabolites. The activity of naltrexone is due to both the parent and 6- $\beta$ -naltrexol metabolite (Meyer et al. 1984). Separate blood samples for PK analysis of acamprosate and for PK analysis of naltrexone and 6- $\beta$ -naltrexol were collected during each treatment period as follows: Day 1 prior to the

first dose of study drug, i.e., baseline; Days 5 and 6, pre-morning dose, i.e. PK trough concentrations; Day 7 pre-morning dose and 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, and 96 h after the Day 7 morning dose.

### Bioanalytical Methods

Naltrexone and 6- $\beta$ -naltrexol plasma concentrations were measured using a validated high performance liquid chromatographic mass spectrometric analytical method with a lower limit of quantification set at 0.25 ng/mL (Beyerlein and Polywacz 1998). The variability of back-calculated concentrations of calibration standards ranged from 4.0% to 9.4% for naltrexone. The between-day precision was determined at levels of 0.750, 7.50, 80.0 and 250 ng/mL in replicate analyses ( $n = 36, 36, 60$  and  $12$ , respectively). The between-day variability did not exceed 14.3%. The relative standard deviation (RSD) for the back-calculated concentration for naltrexone was 5.4% with a deviation of  $-1.2\%$  from the theoretical concentration. For 6- $\beta$ -naltrexol, the RSD for the back-calculated concentration was 3.4% with a deviation of 0.5% from the theoretical concentration.

Acamprosate plasma concentrations were measured by a validated gas chromatography/negative ion chemical ionization mass spectrometry method with a lower limit of quantification of 3.12 ng/mL (Girault et al. 1990). At this level, the precision (% RSD) and accuracy (mean percentage of error), calculated from 10 replicate samples were equal to 4.36% and 0.87% respectively. The between-day precision was determined at levels of 6.25, 50, and 400 ng/mL in replicate analyses. The RSD values were lower than 6.53% and the accuracy was between  $-0.83\%$  and 2.45%.

For each subject, the following pharmacokinetic parameters were determined for naltrexone, 6- $\beta$ -naltrexol, and acamprosate using plasma concentration-time profiles on Day 7 according to the model independent approach with Win Nonlin Professional Version 1.5 software (Scientific Consultant, Inc.): maximum observed (peak) concentration ( $C_{max}$ ); time to maximum concentration ( $T_{max}$ ); degree of fluctuation at steady state (DF); area under the plasma concentration-time curve over one dosing interval, i.e., from hours 0 to 12 for acamprosate and hours 0 to 24 for naltrexone and 6- $\beta$ -naltrexol, estimated by linear trapezoidal rule ( $AUC_{0-\tau}$ ); and apparent plasma terminal phase elimination half-life ( $T_{1/2}$ ).

### Tests of Cognitive Functioning

A pharmacodynamic drug interaction was evaluated with the Cognitive Drug Research computerized assessment system that assesses drug effects on various parameters of cognitive functioning, e.g., word recall, word recognition, attention and reaction time (Wesnes et al. 1991, 1994, 2000). All tasks are computer con-

trolled, with stimuli presented on high-resolution monitors, and the responses recorded via two buttons, one marked 'NO' and the other 'YES'.

Tasks assessing reaction time (Simple Reaction Time, Choice Reaction Time) or speed of performance (Numeric Working Memory, Delayed Word Recognition) were measured in milliseconds. Tasks assessing the accuracy of performance (Immediate and Delayed Word Recall, Digit Vigilance) were scored as the percent of possible correct responses. Additionally, a Sensitivity Index was calculated for Numeric Working Memory and Delayed Word Recognition in which the ability to identify previously presented items was assessed relative to the ability to correctly reject "distracter" items which were not previously presented. A score of 1 represents perfect sensitivity to the task information: all previously presented items are correctly identified and all distracter items are rejected as novel. A score of zero represents chance performance or insensitivity to task information.

Subjects completed four training sessions. Subjects were tested during each treatment period at check in, on Days 1, 3, and 7 at pre-dose, 4 and 7 h post-dose, and on Day 11 prior to discharge. Parallel forms of tests were presented in each testing session to control for practice effects. As a secondary endpoint, results from the 4-hour post-dose testing session were evaluated in relation to PK effects from the same timepoint.

### Sample Size Determination

A primary objective of this study was to test for a pharmacokinetic drug interaction between oral doses of acamprosate and naltrexone. Sample size calculations for acamprosate were based on summarized data from a 2-way crossover study of repeated doses of acamprosate using within-subject variability data (Lipha Pharmaceuticals, Inc. 1996). Naltrexone calculations were based on summarized data from a 4-way crossover study of varying doses of naltrexone using between-subject variability data (Meyer et al. 1984). A sample size of 24 in a crossover design which uses within-subject variance as compared with the between-subject variance of other designs was estimated to have at least 90% power ( $\alpha = 0.05$ ) to detect mean percentage changes of 20% for acamprosate AUC and 20% for naltrexone AUC.

### Statistical Analyses

Statistical significance for selected pharmacokinetic parameters was assessed using an analysis of variance (ANOVA) model with terms for sequence, subject within sequence, period, and treatment. In addition to ANOVAs on untransformed data, ANOVAs were done on natural log (ln) transformed  $C_{max}$  and  $AUC_{0-\tau}$  data. The ln transformed results were the pivotal criterion

used to draw conclusions regarding drug interaction, and due to large variability in  $C_{\max}$ ,  $AUC_{0-\tau}$  was the primary variable analyzed. Since the  $T_{\max}$  data were not normally distributed, they were compared using the Friedman's nonparametric test (Sokal and Rohlf 1995).

To assess if naltrexone or 6- $\beta$ -naltrexol had an effect on acamprosate and if acamprosate had an effect on naltrexone or 6- $\beta$ -naltrexol, per FDA recommendations, 90% confidence intervals (two 1-sided tests) were computed for the difference between the test (co-dosing) and reference (acamprosate or naltrexone alone) values for  $C_{\max}$  and  $AUC_{0-\tau}$  (Steinijans et al. 1991). For  $C_{\max}$  and  $AUC_{0-\tau}$ , no drug interaction effect was assumed if the 90% confidence interval was between 80% and 120%. For the Ln-transformed  $C_{\max}$  and  $AUC_{0-\tau}$ , no drug interaction effect was assumed if the 90% confidence interval was between 80% and 125%.

Steady state levels of acamprosate are achieved by the seventh day of dosing. Therefore, the trough concentrations ( $C_{\min}$ ) observed on Days 5, 6, and 7 were compared by ANOVA to check the equilibrium achievement.

To test for pharmacodynamic drug interactions between acamprosate and naltrexone, the pre-dose cognitive assessment on Day 1 was used as a baseline, and subtracted from subsequent scores to derive difference from baseline scores. The post-dose difference scores were then subject to an ANOVA, terms being fitted for treatment, the repeated assessments, and the interaction between the treatment conditions and repeated assessments. Where the main effect or the interaction was significant, the least squares means procedure was used to make multiple comparisons between the conditions to identify where the differences lay.

Fisher exact test probabilities were calculated for frequency analysis of adverse drug experiences between test and reference groups.

All statistical tests were two-sided and had an  $\alpha$  level of .05.

## RESULTS

### Subjects

Twenty-five subjects entered the study, and 24 completed all three treatment periods. One subject became noncompliant with meal and daily task requirements in the first treatment period and was replaced with a subject who completed the three treatments in the originally assigned sequence. Data for the replaced subject were included in the demographic and safety analysis. The double-blind was maintained for all subjects across all treatment conditions. Subjects (19 males and six females) were a mean age of 31.8 ( $\pm$  5.2) years, 175.3 ( $\pm$  8.9) cm tall, and 74.5 ( $\pm$  8.9) kg in weight. The sample consisted of 23 Caucasian, one Hispanic, and one African American subject.

### Acamprosate Pharmacokinetics

Coadministration of naltrexone significantly enhanced the rate and extent of acamprosate bioavailability, resulting in significantly shorter acamprosate  $T_{\max}$  and higher  $C_{\max}$  values, in comparison with administration of acamprosate alone (Table 1). Acamprosate median  $T_{\max}$  values were 6.0 h following dosing alone and 4.0 h following dosing in combination with naltrexone ( $p < .01$ ). The mean acamprosate  $C_{\max}$  when administered in combination with naltrexone (517 ng/mL) was approximately 33% higher than the mean  $C_{\max}$  when administered alone (390 ng/mL,  $p < .01$ ), and the 90% confidence interval for the test/reference ratio for the Ln-transformed  $C_{\max}$  (120% to 156%) was not entirely contained within the 80% to 125% range, indicating that administration of acamprosate in combination with naltrexone significantly increased the rate of absorption of acamprosate.

The mean acamprosate  $AUC_{0-\tau}$  when administered in combination with naltrexone (4,658 ng hr/mL) was approximately 25% greater than the mean  $AUC_{0-\tau}$  when acamprosate was administered alone (3,734 ng hr/mL). Likewise, the 90% confidence interval for the test/reference ratio for the Ln-transformed  $AUC_{0-\tau}$  (114% to 143%) was not entirely contained within the 80% to 125% range, indicating that administration of acamprosate in combination with naltrexone significantly improved the absorption of acamprosate (Figure 1).

Naltrexone did not significantly affect the elimination half-life of acamprosate. Acamprosate was slowly eliminated following oral administration with mean  $T_{1/2}$  values of 18.5 and 17.9 h when administered alone or in combination with naltrexone, respectively.

Steady-state was verified for acamprosate by ANOVA of trough concentrations from Days 5, 6 and 7, both when administered alone (Day 5 = 264  $\pm$  128.4 ng/mL, Day 6 = 271  $\pm$  123.7 ng/mL, Day 7 = 256  $\pm$  120.9 ng/mL,  $F_{2,23} = 0.48$ ,  $p = .62$ ) and in combination with naltrexone (Day 5 = 336  $\pm$  153.0 ng/mL, Day 6 = 332  $\pm$  148.5 ng/mL, Day 7 = 344  $\pm$  147.4 ng/mL,  $F_{2,23} = 0.18$ ,  $p = .83$ ).

### Naltrexone and 6- $\beta$ -Naltrexol Pharmacokinetics

Co-administration of acamprosate and naltrexone had no effect on the pharmacokinetics of naltrexone and its metabolite, 6- $\beta$ -naltrexol. The 90% confidence intervals for the Ln-transformed  $C_{\max}$  and AUC for naltrexone and 6- $\beta$ -naltrexol are entirely contained within the 80–125% range (Table 1, Figure 2). Acamprosate also had no effect on the elimination half life of naltrexone or 6- $\beta$ -naltrexol.

Steady state analysis was only performed for 6- $\beta$ -naltrexol, as all the trough concentrations for naltrexone, which has an elimination half life of about 4 h (Table 1), were below the limit of quantitation. Steady state

# 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.