

VERSION v4

# Standard Operating Procedure



E-Merge tech Global Services Pvt Ltd

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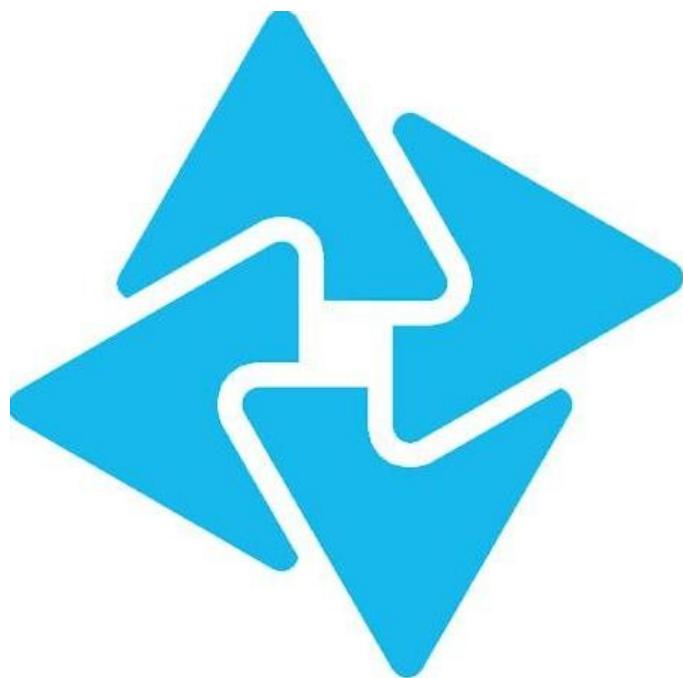
The CEO is a Member of PIUG, IEEE, AUTM & LES

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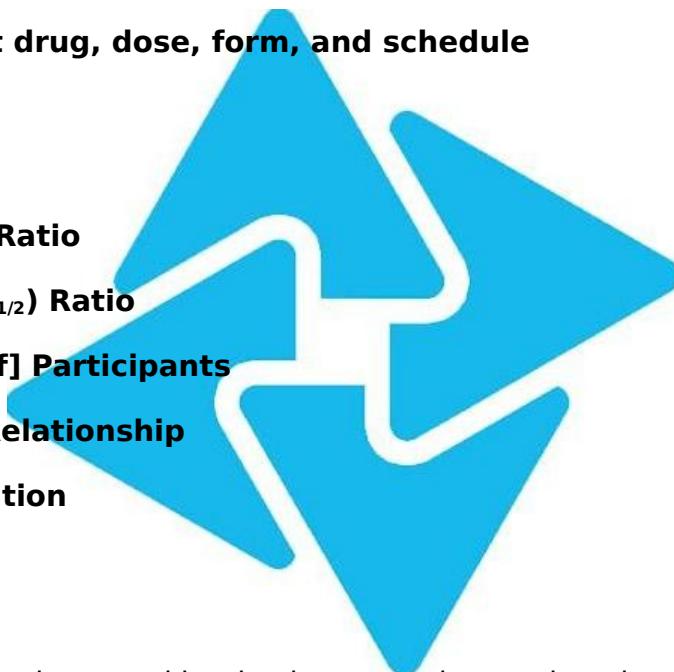
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## 1. Purpose

The purpose of this document is to provide instructions for the manual annotation using DBMI-Annotator tool. The purpose of the project is to extract Pharmacokinetic data from the given set of publications. The following major Pharmacokinetic information should be extracted:

- **Claim**
- **Object drug, dose, form, and schedule**
- **Precipitant drug, dose, form, and schedule**
- **AUC Ratio**
- **C<sub>max</sub> Ratio**
- **Clearance Ratio**
- **Half-life (T<sub>1/2</sub>) Ratio**
- **[Number of] Participants**
- **Evidence Relationship**
- **Randomization**



## 2. Scope

The scope of this pharmacokinetic data curation project is to identify the drug interaction data and its effects. There will be two types of drugs discussed in most of the cases; these are Object Drug and Precipitant Drug.

## 3. Source

- ✓ List of publications provided to E-Merge tech by University of Pittsburgh.

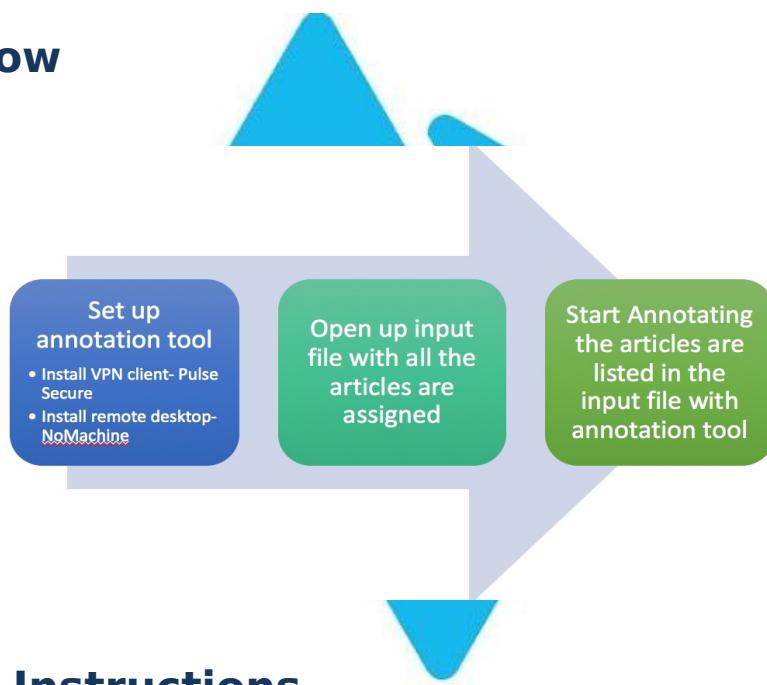
## 4. Definitions

- **Claim:** An assertion about a relationship between entities in the domain of discourse (in this case drug-drug interactions) that is supported or refuted by evidence. The word claim in this context is a generally synonymous with assertion though the latter is used more often to describe a claim's logical formalization.
- **Object Drug:** The drug whose action is altered by the interaction
- **Precipitant Drug:** The drug that causes the altered action of the altered drug
- **AUC:** (Definite Integral) is the plot of concentration of drug in blood plasma against time. Usually it is calculated from the start of the administration of the drug till the drug concentration becomes negligible
- **AUC Ratio:** The ratio of the AUC (as fold or percent increase or decrease) of the object drug in the presence of the purported precipitant drug
- **C<sub>max</sub>:** It is defined as maximum (or peak) serum concentration that a drug achieves in a specified compartment or test area of the body after the drug has been administrated and prior to the administration of a second dose
- **C<sub>max</sub> Ratio:** The ratio of the C<sub>max</sub> (as fold or percent increase or decrease) of the object drug in the presence of the purported precipitant drug
- **T<sub>1/2</sub>:** (Half life) The duration of action of the drug is known as Half-life. This is the time period required by the drug to reach its concentration or amount to half
- **T<sub>1/2</sub> Ratio:** The ratio of the T<sub>1/2</sub> (as fold or percent increase or decrease) of the object drug in the presence of the purported precipitant drug
- **Clearance:** The rate at which a drug is removed from the plasma is known as clearance



- **Clearance Ratio:** The ratio of the Clearance (as fold or percent increase or decrease) of the object drug in the presence of the purported precipitant drug
- **Number of participants:** The number of participants entered into a clinical trial. (Note: this is different than number of participants who complete, which is participants - dropouts)
- **Evidence Relationship:** If the evidence supports or refuses the claim.
- **Randomization:** 'Yes' if the study randomized participants to exposure or order of exposure

## 5. Work Flow



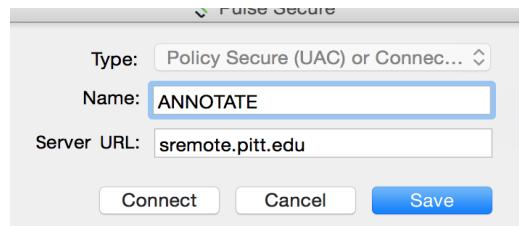
## 6. General Instructions

E-Merge tech will be provided with an input spreadsheet and access to an online annotation interface:

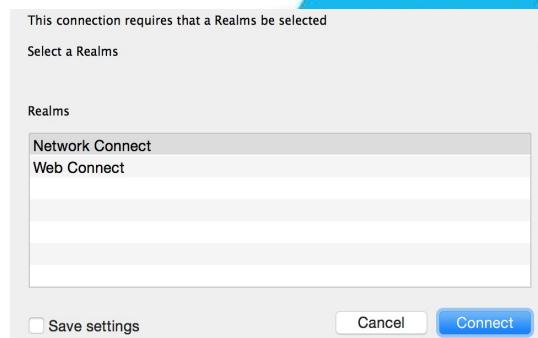
1. **Set Up Annotation Tool:** The web interface used for annotation
  - (1) Install VPN client and remote into our network.
    - Install VPN client (Pulse Secure) on your computer



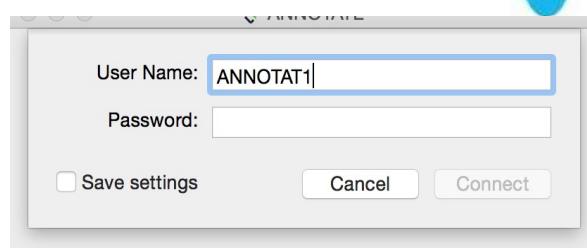
- Open up Pulse Secure and add a connection like below



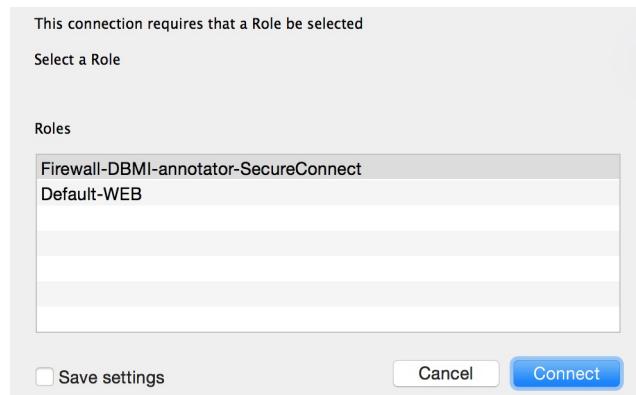
- Click Connect to continue and select Network Connect to continue



- Type in the username “ANNOTAT1” and password to connect



- Select VPN role “Firewall-DBMI-annotator-SecureConnect” and click connect



*Note: We'll have 5 accounts for you later to do annotations. The current one is just for testing.*

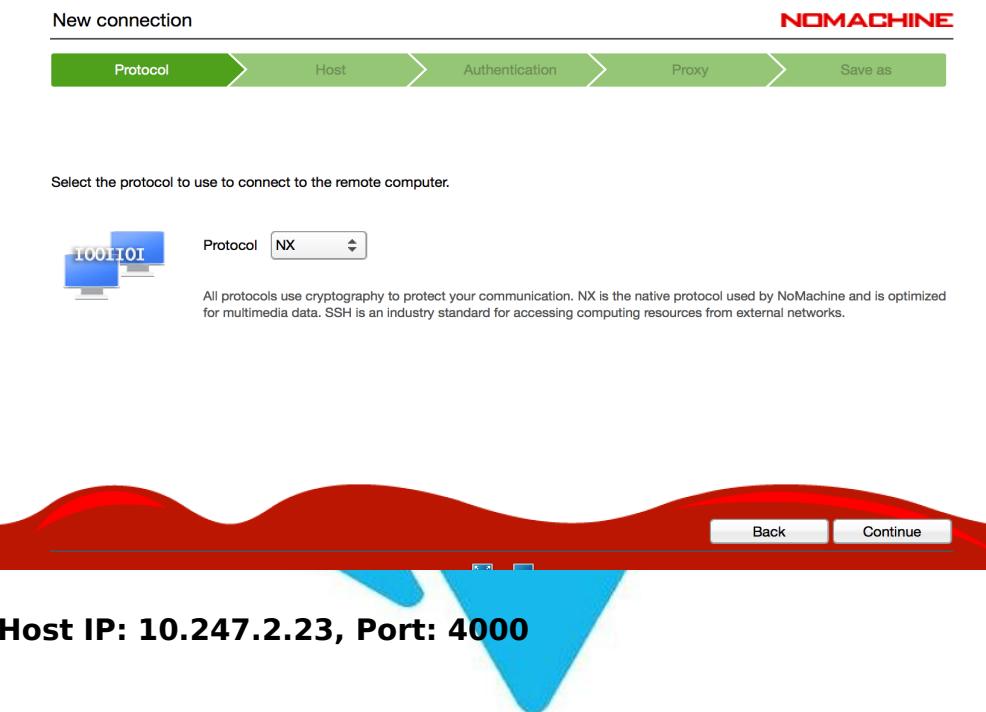
(2) Install remote desktop

- Download NoMachine as the remote desktop tool from  
<https://www.nomachine.com>





- Open up NoMachine to create a new connection after installation. Here are the connection information: **Protocol: NX**





New connection

NOMACHINE

Protocol > Host > Authentication > Proxy > Save as

Insert the hostname or IP and port where you want to connect.



Host 10.247.2.23

Port 4000

The port was chosen automatically based on the default for the protocol. If the remote computer was configured to listen on a different port, please insert it above.

Use UDP communication for multimedia data

Back Continue

## Authentication method: password

New connection

NOMACHINE

Protocol > Host > Authentication > Proxy > Save as

Choose which authentication method you want to use.



Password  
Use password authentication.



Private key  
Use key-based authentication with a key you provide.



Kerberos  
Use Kerberos ticket-based authentication.

Back Continue

## Proxy: Don't use a proxy



New connection

NOMACHINE

Protocol

Host

Authentication

Proxy

Save as

Use a HTTP proxy for the network connection.



Don't use a proxy

Choose this if you are connecting to a computer on your same LAN or if you are on a residential broadband connection.



Connect using a HTTP proxy

Use a proxy if you are connecting to a computer outside your LAN from a corporate network where external access is protected by a firewall.

Back Continue

- After you click continue, please click yes if there is any warning box pops up. Then, type in username “ annotat1” and password to log in VLAN server

Connection to 10.247.2.23

NOMACHINE

Please type your username and password to login.



Username

annotat1

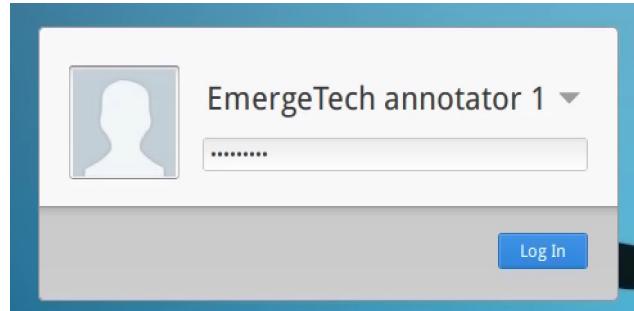
Password

Save this password in the connection file

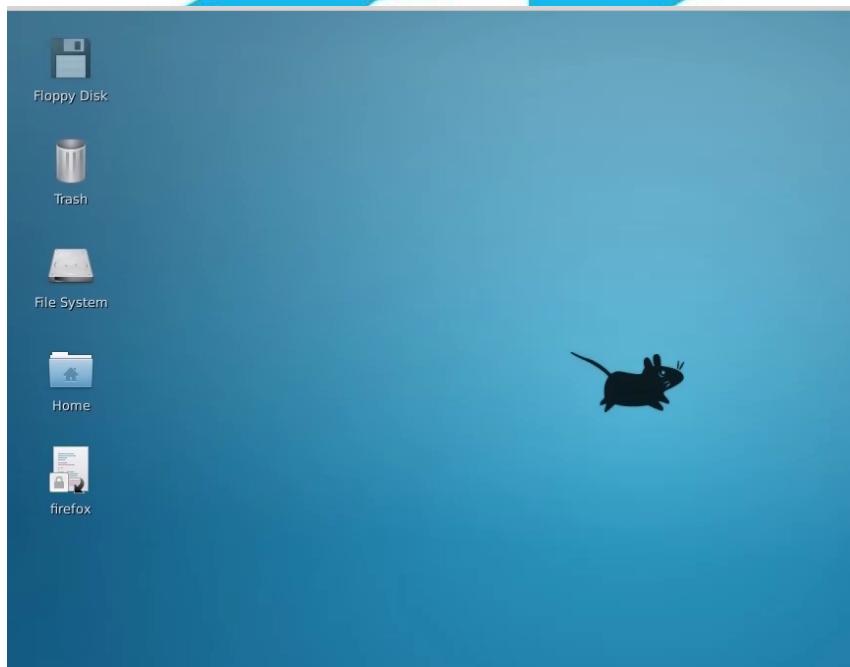
Back OK



- A screen will be available after you log in to the server.

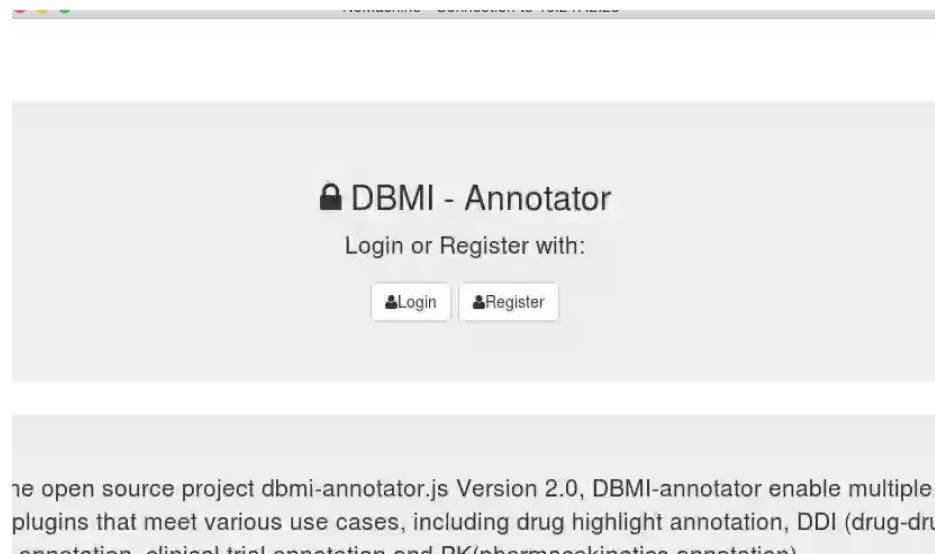


- Please click the icon “firefox” to open up firefox web browser.





- Then you can type in the url <http://localhost/dbmiannotator> to access our annotator tool. If you see an interface like this on the screen, congratulation, you access the annotation tool successfully.



- (3) After you see the login page, click login button and type in the username "test@gmail.com" and password to start the work.
- (4) The next step is to open up the input file, find the articles are assigned and annotate their information using the annotation tool.
2. **Open Up Input File:** The file lists all the articles and information are needed for doing annotations. To open up the input file, please type this url <http://10.247.2.23:3000/mp-testing-case/PMC-Articles.html> into a new tab on the same firefox browser and follow the process on next page.



1	No.	Article Link	Article	Status	Study Type	This is evidence	Drug	Prop
2	1	<a href="http://localhost/dbmiannotator/PMC1884180.html">http://localhost/dbmiannotator/PMC1884180.html</a>	Cooper_2003_125346 Amy completed on July 22nd, 45		clinical study	Against	ketoconazole	interacts_with
3	2	<a href="http://localhost/dbmiannotator/PMC3922121.html">http://localhost/dbmiannotator/PMC3922121.html</a>	DeGorter_2013_23876492			For	Rosuvastatin	substrate_of
4			DeGorter_2013_23876492			For	Atorvastatin	substrate_of
5			Hsyu_2001_11709322		clinical study	For	Nelfinavir	interacts_with
6			Hsyu_2001_11709322		clinical study	For	Nelfinavir	interacts_with
7			Hsyu_2001_11709322		clinical study	Against	Simvastatin	interacts_with
8		<a href="http://localhost/dbmiannotator">http://localhost/dbmiannotator</a>						

## Process

(1) Check input column *Meets Inclusion Criteria* of the Input spreadsheet. Annotate **only** if the inclusion criteria said Yes.

This is evidence	Drug	Property	Value (drop down - for non-quantitative assertions)	Meets Inclusion Criteria?
Against	ketoconazole	interacts_with	Rosuvastatin	Yes
For	Rosuvastatin	substrate_of	OATP1B1	Needs to be evaluated
For	Atorvastatin	substrate_of	OATP1B1	Needs to be evaluated
For	Nelfinavir	interacts_with	Atorvastatin	Yes
For	Nelfinavir	interacts_with	Simvastatin	Yes

(2) In the annotation interface, find the article needs to be annotated and open its article link listed in input column *Article Link*

For example: Article (Cooper\_2003\_12534645),

Article Link(<http://localhost/dbmiannotator/PMC1884190.html>)

No.	Article Link	Article	Status	Study Type	This is evidence
1	<a href="http://localhost/dbmiannotator/PMC1884190.html">http://localhost/dbmiannotator/PMC1884190.html</a>	Cooper_2003_12534645	Amy completed on July 22nd.	clinical study	Against
2	<a href="http://localhost/dbmiannotator/PMC3922121.html">http://localhost/dbmiannotator/PMC3922121.html</a>	DeGorter_2013_23876492			For
		DeGorter_2013_23876492			For
		Hsyu_2001_11709322		clinical study	For
		Hsyu_2001_11709322		clinical study	For

**Note: the table below explains all the information is needed by annotation tool and the columns in the input file.**

Information is needed by	Information location in input file
Whether to annotate	Column: Meets inclusion criteria?
Article to be annotated	Column: Article
Main Claim	Column: The sentence(s) that state the main
Drug1	Column: Drug
Relationship	Column: Property
Method type	Clinical Trial
Drug2/inhibitor	Column: Value (drop down - for non-
Participants	Column: The sentence(s), table(s), and/or figure(s) that specify the methods and Column: The sentence(s), table(s), and/or figure(s) that specify the participants
AUC Ratio, Cmax Ratio, Clearance Ratio, and/or Half-life (T1/2) Ratio	Column: The sentence(s), table(s), and/or figure(s) that specify the results
Ev_relationship (evidence relationship)	Column: This is evidence. If it's an "against", then selects "refuse", otherwise selects "support"

(3) In the annotation interface, find the article needs to be annotated and open its article link listed in input column *Article Link*



[Close] [Minimize] [Maximize]

## **Comparative Pharmacokinetic Interaction Profiles of Pravastatin, Simvastatin, and Atorvastatin When Coadministered With Cytochrome P450 Inhibitors**

Terry A. Jacobson, MD

**Three-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (statins) are first-line treatments for hypercholesterolemia. Although exceedingly well tolerated, treatment with statins incurs a small risk of myopathy or potentially fatal rhabdomyolysis, particularly when coadministered with medications that increase their systemic exposure.** Studies compared the multiple-dose pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with 4 inhibitors of cytochrome P450-3A4 isozymes in healthy subjects. Compared with pravastatin alone, coadministration of verapamil, mibepradil, or itraconazole with pravastatin was associated with no significant changes in pravastatin pharmacokinetics. However, concomitant verapamil increased the simvastatin area under the concentration-time curve (AUC) approximately fourfold, the maximum serum concentration ( $C_{max}$ ) fivefold, and the active metabolite simvastatin acid AUC and  $C_{max}$  approximately four- and threefold, respectively [all comparisons  $p < 0.001$ ]. Similar [greater than fourfold] important increases in these parameters and a >60% increase in the serum half-life ( $p = 0.03$ ) of atorvastatin were observed when coadministered with mibepradil. The half-life of atorvastatin also increased by ~60% ( $p = 0.052$ ) when coadministered with itraconazole, which elicited a 2.4-fold increase in the  $C_{max}$  of atorvastatin and a 47% increase in the AUC [ $p < 0.001$  for  $C_{max}$  and AUC]. Clarithromycin significantly ( $p < 0.001$ ) increased the AUC and  $C_{max}$  of all 3 statins, most markedly simvastatin (~10-fold increase in AUC) and simvastatin acid (12-fold), followed by atorvastatin [greater than fourfold] and then pravastatin (almost twofold). Pravastatin has a neutral drug interaction profile relative to cytochrome P450-3A4 inhibitors, but these substrates markedly increase systemic exposure to simvastatin and atorvastatin. © 2004 by Excerpta Medica, Inc. [Am J Cardiol 2004;94:140–146]

**A**s a pharmacologic class, statins are exceedingly well tolerated. However, rhabdomyolysis remains a serious concern. According to postmarketing surveillance data for the United States, ≤1 case of fatal rhabdomyolysis was reported per 1 million prescriptions of statins, other than cerivastatin and rosuvastatin, up to June 2001.<sup>1</sup> Statin-associated myopathy is a dose-related phenomenon; its incidence increases about fivefold (from ~0.3% to ~1.5%) when certain statins (e.g., lovastatin, simvastatin, or atorvastatin) are coadministered with medications that share their metabolic pathways and/or increase their systemic exposure.<sup>2,3</sup> These include lipid-lowering agents such as fibrates<sup>4</sup> (especially gemfibrozil), calcium channel blockers,<sup>5,6</sup> immunosuppressive agents (e.g., cyclosporine)<sup>7,8</sup> macrolide antibiotics (e.g., clarithromycin)<sup>9,12</sup> imidazole antifungal agents (e.g., itraconazole),<sup>13–16</sup> protease inhibitors for human immunodeficiency virus,<sup>17</sup> and combinations of these and other drugs,<sup>18–21</sup> including over-the-counter agents and grapefruit juice.<sup>22</sup> To delineate the potential for pharmacokinetic interactions between pravastatin, simvastatin, or atorvastatin when coadministered with cytochrome P450 (CYP) 3A4 inhibitors, multiple-dose studies were conducted in healthy subjects.

**METHODS**

**Overview of study designs:** This report summarizes data from 4 small, short-term parallel-group studies that evaluated the effects of CYP3A4 inhibitors on the multiple-dose pharmacokinetics of statins in 4 groups of healthy subjects. These studies, which were conducted from January 6, 1998 through April 4, 1998, evaluated the pharmacokinetics of (1) 40 mg of pravastatin or 40 mg of simvastatin when coadministered with 480 mg of extended-release verapamil; (2) 40 mg of pravastatin or 80 mg of atorvastatin when coadministered with 100 mg of mibepradil; (3) 40 mg of pravastatin or 80 mg of atorvastatin when coadministered with 200 mg of itraconazole; and (4) 40 mg of pravastatin, 40 mg of simvastatin, or 80 mg of atorvastatin when coadministered with 500 mg of clarithromycin twice daily.

All agents were dispensed as marketed products by the investigators. The studies described in this report were conducted at the IBRD Center for Clinical Research (Neptune, New Jersey) for the verapamil, mi-

From the Office of Health Promotion and Disease Prevention, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia. This work was supported by Biogen/Meyen-Suska Co., Princeton, New Jersey. Manuscript accepted February 9, 2004; revised manuscript received and accepted July 14, 2004.

Address for reprints: Terry A. Jacobson, MD, Department of Medicine, Emory University School of Medicine, 479 Jesse Hill Jr. Drive, Atlanta, Georgia 30303. Email: jaco02@emory.edu.

**doi:10.1016/j.amjcard.2004.07.080 has been loaded**

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**Some drug names may already be highlighted in yellow; these have been pre-annotated by a computer tool.**

(4) Select the claim.

4(a) First find the appropriate information in the input document: Input column *The sentence(s) that state the main assertion* specifies either a page location or a textual quotation. Find this text by going to the page location, reading through the document, or by hitting Ctrl-F and searching for the sentence.

4(b) Highlight *the sentence(s) that state the main assertion*, then click the “MP” button.



Three-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (statins) are first-line treatments for hypercholesterolemia. Although exceedingly well tolerated, treatment with statins incurs a small risk of myopathy or potentially fatal rhabdomyolysis, particularly when co-administered with medications that increase their systemic exposure. Studies compared the multiple-dose pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with 4 inhibitors of cytochrome P450-3A4 isoenzymes in healthy subjects. Compared with pravastatin alone, co-administration of verapamil, mibepradil, or itraconazole with pravastatin was associated with no significant changes in pravastatin pharmacokinetics. However, concomitant verapamil increased the simvastatin area under the concentration:time curve (AUC) approximately fourfold, the maximum serum concentration ( $C_{max}$ ) five-fold, and the active metabolite simvastatin acid AUC and

comparisons  $p < 0.001$ ). Similar (greater than fourfold) important increases in these parameters and a  $>60\%$  increase in the serum half-life ( $p = 0.03$ ) of atorvastatin were observed when coadministered with mibepradil. The half-life of atorvastatin also increased by  $\approx 60\%$  ( $p = 0.052$ ) when coadministered with itra elicit a 2.4-fold increase in the  $C_{max}$  Drug and a 47% increase in the AUC ( $p < 0.001$ ). Clarithromycin significantly ( $p < 0.001$ ) increased the AUC (and  $C_{max}$ ) of all 3 statins, most markedly simvastatin ( $\sim 10$ -fold increase in AUC) and simvastatin acid (12-fold), followed by atorvastatin (greater than fourfold) and then pravastatin (almost twofold). Pravastatin has a neutral drug interaction profile relative to cytochrome P450-3A4 inhibitors, but these substrates markedly increase systemic exposure to simvastatin and atorvastatin. ©2004 by Excerpta Medica, Inc.

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4(c) Next click “create a claim”

Three-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (statins) are first-line treatments for hypercholesterolemia. Although exceedingly well tolerated, treatment with statins incurs a small risk of myopathy or potentially fatal rhabdomyolysis, particularly when co-administered with medications that increase their systemic exposure. Studies compared the multiple-dose pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with 4 inhibitors of cytochrome P450-3A4 isoenzymes in healthy subjects. Compared with pravastatin alone, co-administration of verapamil, mibepradil, or itraconazole with pravastatin was associated with no significant changes in pravastatin pharmacokinetics. However, concomitant verapamil increased the simvastatin area under the concentration:time curve (AUC) approximately fourfold, the maximum serum concentration ( $C_{max}$ ) five-fold, and the active metabolite simvastatin acid AUC and

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(5) Next we need to enter the text associated with this claim into the annotation



interface.

5(a) First gather the required information from the input document, as follows:

- Drug 1. See Column “Drug”
- The property, or relationship. See Column “Property”
- Drug 2 or inhibitor. See Column “Value (drop down - for non-quantitative assertions)”
- The method. Currently, there is only one method – Clinical Trial.

5(b) Second, select the drug name (from input column *Drug*), relationship (from input column *Property*), and method (Clinical Trial). Note that “save” is greyed out because more information is needed

*Three hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are first-line treatments for hypercholesterolemia. Although exceedingly well tolerated, treatment with statins incurs a small risk of myopathy or potentially fatal rhabdomyolysis, particularly when co-administered with medications that increase their systemic exposure. Studies compared the multiple-dose pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with 4 inhibitors of cytochrome P450-3A4 isoenzymes in healthy subjects. Compared with pravastatin alone, co-administration of verapamil, mibepradil, or itraconazole with pravastatin was associated with no significant changes in pravastatin pharmacokinetics. However, concomitant verapamil increased the simvastatin area under the concentration:time curve (AUC) approximately 5-fold. Coadministration of mibepradil or itraconazole with atorvastatin resulted in important increases in these parameters and a >60% increase in the serum half-life ( $p = 0.03$ ) of atorvastatin were observed when coadministered with mibepradil. The half-life of atorvastatin also increased by ~60% ( $p = 0.052$ ) when coadministered with itraconazole, which elicited a 2.4-fold increase in the  $C_{max}$  of atorvastatin and a 47% increase in the AUC ( $p < 0.001$  for  $C_{max}$  and AUC). Clarithromycin significantly ( $p < 0.001$ ) increased the AUC (and  $C_{max}$ ) of all 3 statins, most markedly simvastatin (~10-fold increase in AUC) and simvastatin acid (12-fold), followed by atorvastatin (greater than fourfold) and then pravastatin (almost twofold). Pravastatin has a neutral drug interaction profile relative to cytochrome P450-3A4 inhibitors, but these substrates markedly increase systemic exposure to simvastatin and atorvastatin. ©2004 by Excerpta Medica, Inc.*

Annotator Editor	Annotator Table	$C_{max}$ , five-, AUC and
Claim		
Drug1 <input type="text" value="clarithromycin"/> ▾	Relationship <input type="text" value="interacts with"/> ▾	Method <input type="text" value="clinical trial"/> ▾
<input type="button" value="cancel"/>	<input type="button" value="save"/>	

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5(c) The Drug2 box appears; enter the second drug (from input column “Value (drop down - for non-quantitative assertions)”).



3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (statins) are first-line treatments for hypercholesterolemia. Although exceedingly well tolerated, treatment with statins incurs a small risk of myopathy or potentially fatal rhabdomyolysis, particularly when co-administered with medications that increase their systemic exposure. Studies compared the multiple-dose pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with 4 inhibitors of cytochrome P450-3A4 isoenzymes in healthy subjects. Compared with pravastatin alone, coadministration of verapamil, mibepradil, or itraconazole with pravastatin was associated with no significant changes in pravastatin pharmacokinetics. However, concomitant verapamil increased the simvastatin area under the concentration:time curve (AUC) approximately

comparisons  $p < 0.001$ ). Similar (greater than fourfold) important increases in these parameters and a  $>60\%$  increase in the serum half-life ( $p = 0.03$ ) of atorvastatin were observed when coadministered with mibepradil. The half-life of atorvastatin also increased by  $\approx 60\%$  ( $p = 0.052$ ) when coadministered with itraconazole, which elicited a 2.4-fold increase in the  $C_{max}$  of atorvastatin and a 47% increase in the AUC ( $p < 0.001$  for  $C_{max}$  and AUC). Clarithromycin significantly ( $p < 0.001$ ) increased the AUC (and  $C_{max}$ ) of all 3 statins, most markedly simvastatin ( $\sim 10$ -fold increase in AUC) and simvastatin acid (12-fold), followed by atorvastatin (greater than fourfold) and then pravastatin (almost twofold). Pravastatin has a neutral drug interaction profile relative to cytochrome P450-3A4 inhibitors, but these substrates markedly increase systemic exposure to simvastatin and atorvastatin. ©2004 by Excerpta Medica, Inc.

Annotator Editor	Annotator Table	$C_{max}$	fiveday AUC and	
Claim				
Drug1	clarithromycin	<input type="radio"/> Precipitant	Relationship interacts with	Method clinical trial
Drug2	atorvastatin	<input checked="" type="radio"/> Precipitant		
<input type="button" value="cancel"/>		<input type="button" value="save"/>		

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5(d) Indicate which drug is the precipitant by clicking the radio button labeled "Precipitant".

5(e) Click "Save".

5(f) A popup appears asking what you would like to do, for this text span.

- add another claim
- add material/data for an existing claim
- finish with this span, move on

Select one of these options and click "OK".

In this case we want to add another claim for the same text span.

This would be indicated when the SAME filename listed in input *Column: Article* has multiple rows, where those rows have the SAME text/location specified in input *Column: The sentence(s) that state the main assertion*.

Therefore, we click "add another claim"



3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are first-line treatments for hypercholesterolemia. Although exceedingly well tolerated, treatment with statins incurs a small risk of myopathy or potentially fatal rhabdomyolysis, particularly when co-administered with medications that increase their systemic exposure. Studies compared the multiple-dose pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with 4 inhibitors of cytochrome P450-3A4 isoenzymes in healthy subjects. Compared with pravastatin alone, co-administration of verapamil, mibepradil, or itraconazole with pravastatin was associated with no significant changes in pravastatin concomitant verapamil increased the simvastatin area under the concentration-time curve (AUC) approximately

comparisons  $p < 0.001$ , similar (greater than fourfold, important increases in these parameters and a  $>60\%$  increase in the serum half-life ( $p = 0.03$ ) of atorvastatin were observed when coadministered with mibepradil. The half-life of atorvastatin also increased by  $\approx 60\%$  ( $p = 0.052$ ) when coadministered with itraconazole, which elicited a 2.4-fold increase in the  $C_{max}$  of atorvastatin and a 47% increase in the AUC ( $p < 0.001$  for  $C_{max}$  and AUC). Clarithromycin significantly ( $p < 0.001$ ) increased the AUC (and  $C_{max}$ ) of all 3 statins, most markedly simvastatin ( $\sim 10$ -fold increase in AUC) and simvastatin acid (12-fold), followed by atorvastatin (greater than fourfold) and then pravastatin (almost twofold). Pravastatin has a neutral drug interaction profile relative to cytochrome P450-3A4 inhibitors, but these substrates markedly increase systemic exposure to simvastatin and atorvastatin. ©2004 by Excerpta Medica, Inc.

Annotator Editor

Drug1 clarithromycin

Drug2 atorvastatin

Add data to the same text span for claim  
clarithromycin interacts with atorvastatin | ▾ OK

Add another claim to the same text span | ▾ OK

Move to a different text span (finish) | ▾ OK

cancel save

## (6) We repeat step 4 in order to add the second claim.

3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are first-line treatments for hypercholesterolemia. Although exceedingly well tolerated, treatment with statins incurs a small risk of myopathy or potentially fatal rhabdomyolysis, particularly when co-administered with medications that increase their systemic exposure. Studies compared the multiple-dose pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with 4 inhibitors of cytochrome P450-3A4 isoenzymes in healthy subjects. Compared with pravastatin alone, co-administration of verapamil, mibepradil, or itraconazole with pravastatin was associated with no significant changes in pravastatin pharmacokinetics. However, concomitant verapamil increased the simvastatin area under the concentration-time curve (AUC) approximately

comparisons  $p < 0.001$ , similar (greater than fourfold, important increases in these parameters and a  $>60\%$  increase in the serum half-life ( $p = 0.03$ ) of atorvastatin were observed when coadministered with mibepradil. The half-life of atorvastatin also increased by  $\approx 60\%$  ( $p = 0.052$ ) when coadministered with itraconazole, which elicited a 2.4-fold increase in the  $C_{max}$  of atorvastatin and a 47% increase in the AUC ( $p < 0.001$  for  $C_{max}$  and AUC). Clarithromycin significantly ( $p < 0.001$ ) increased the AUC (and  $C_{max}$ ) of all 3 statins, most markedly simvastatin ( $\sim 10$ -fold increase in AUC) and simvastatin acid (12-fold), followed by atorvastatin (greater than fourfold) and then pravastatin (almost twofold). Pravastatin has a neutral drug interaction profile relative to cytochrome P450-3A4 inhibitors, but these substrates markedly increase systemic exposure to simvastatin and atorvastatin. ©2004 by Excerpta Medica, Inc.

Annotator Editor

Drug1 clarithromycin | ▾

Annotator Table

Relationship interacts with | ▾

Method clinical trial | ▾

Claim

cancel save



Three-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (statins) are first-line treatments for hypercholesterolemia. Although exceedingly well tolerated, treatment with statins incurs a small risk of myopathy or potentially fatal rhabdomyolysis, particularly when co-administered with medications that increase their systemic exposure. Studies compared the multiple-dose pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with 4 inhibitors of cytochrome P450-3A4 isoenzymes in healthy subjects. Compared with pravastatin alone, coadministration of verapamil, mibepradil, or itraconazole with pravastatin was associated with no significant changes in pravastatin pharmacokinetics. However, concomitant verapamil increased the simvastatin area under the concentration:time curve (AUC) approximately

comparisons  $p < 0.001$ ). Similar (greater than fourfold) important increases in these parameters and a >60% increase in the serum half-life ( $p = 0.03$ ) of atorvastatin were observed when coadministered with mibepradil. The half-life of atorvastatin also increased by ~60% ( $p = 0.052$ ) when coadministered with itraconazole, which elicited a 2.4-fold increase in the  $C_{max}$  of atorvastatin and a 47% increase in the AUC ( $p < 0.001$  for  $C_{max}$  and AUC). Clarithromycin significantly ( $p < 0.001$ ) increased the AUC (and  $C_{max}$ ) of all 3 statins, most markedly simvastatin (~10-fold increase in AUC) and simvastatin acid (12-fold), followed by atorvastatin (greater than fourfold) and then pravastatin (almost twofold). Pravastatin has a neutral drug interaction profile relative to cytochrome P450-3A4 inhibitors, but these substrates markedly increase systemic exposure to simvastatin and atorvastatin. ©2004 by Excerpta Medica, Inc.

Annotator Editor	Annotator Table	$C_{max}$	$AUC$	$AUC$	$AUC$
Claim					
Drug1	clarithromycin	<input type="radio"/> Precipitant	Relationship	interacts with	<input type="radio"/> Method
Drug2	pravastatin	<input checked="" type="radio"/> Precipitant			clinical trial
<a href="#">cancel</a>			<a href="#">save</a>		

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In this case we STILL want to add another claim for the same text span.

This would be indicated when the SAME filename listed in input *Column: Article* has multiple rows, where those rows have the SAME text/location specified in input *Column: The sentence(s) that state the main assertion*.

Therefore, we AGAIN click “add another claim”

Annotator Editor		An			
Drug1		clarithromycin	<input type="radio"/>	<input checked="" type="radio"/> Add data to the same text span for claim clarithromycin interacts with atorvastatin	<input type="radio"/> OK
Drug2		pravastatin	<input checked="" type="radio"/>	<input type="radio"/> Add another claim to the same text span	<input type="radio"/> OK
			<input type="radio"/> Move to a different text span (finish)	<input type="radio"/> OK	<input type="radio"/> save
Drug interaction profile relative to 4 inhibitors, but these substrates markedly increase systemic exposure to simvastatin and atorvastatin. ©2004 by Excerpta Medica, Inc.					
©2004 by Excerpta Medica, Inc.					

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(7) We again repeat step 4 for the third claim. There is a small difference because



simvastatin is a substrate; we know this because *Column Property* of the input is "substrate\_of".

7(a) We enter Drug 1 (from input *Column Drug*) and Relationship (from input *Column Property*).

Statins are first-line treatments for hypercholesterolemia. Although exceedingly well tolerated, treatment with statins incurs a small risk of myopathy or potentially fatal rhabdomyolysis, particularly when co-administered with medications that increase their systemic exposure. Studies compared the multiple-dose pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with 4 inhibitors of cytochrome P450-3A4 isoenzymes in healthy subjects. Compared with pravastatin alone, co-administration of verapamil, mibepradil, or itraconazole with pravastatin was associated with no significant changes in pravastatin pharmacokinetics. However, concomitant verapamil increased the simvastatin area under the concentration-time curve (AUC) approximately

important increases in these parameters and a >60% increase in the serum half-life ( $p = 0.03$ ) of atorvastatin were observed when coadministered with mibepradil. The half-life of atorvastatin also increased by ~60% ( $p = 0.052$ ) when coadministered with itraconazole, which elicited a 2.4-fold increase in the  $C_{max}$  of atorvastatin and a 47% increase in the AUC ( $p < 0.001$  for  $C_{max}$  and AUC). Clarithromycin significantly ( $p < 0.001$ ) increased the AUC (and  $C_{max}$ ) of all 3 statins, most markedly simvastatin (~10-fold increase in AUC) and simvastatin acid (12-fold), followed by atorvastatin (greater than fourfold) and then pravastatin (almost twofold). Pravastatin has a neutral drug interaction profile relative to cytochrome P450-3A4 inhibitors, but these substrates markedly increase systemic exposure to simvastatin and atorvastatin. ©2004 by Excerpta Medica, Inc.

Annotator Editor	Annotator Table	$C_{max}$ five AUC and
Claim		
Drug1 <input type="text" value="simvastatin"/> ▾	Relationship <input type="text" value="substrate of"/> ▾	Method <input type="text"/> ▾
cancel	save	

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7(b) Next we add Method, which is Clinical Trial.

7(c) Once we choose "substrate of" for the relationship, and "clinical trial" for the Method, we are prompted for the Enzyme as well as for Drug 2.



3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (statins) are first-line treatments for hypercholesterolemia. Although exceedingly well tolerated, treatment with statins incurs a small risk of myopathy or potentially fatal rhabdomyolysis, particularly when co-administered with medications that increase their systemic exposure. Studies compared the multiple-dose pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with 4 inhibitors of cytochrome P450-3A4 isoenzymes in healthy subjects. Compared with pravastatin alone, coadministration of verapamil, mibepradil, or itraconazole with pravastatin was associated with no significant changes in pravastatin pharmacokinetics. However, concomitant verapamil increased the simvastatin area under the concentration:time curve (AUC) approximately

five-fold (from  $C_{max}$  and AUC and comparisons  $p < 0.001$ ). Similar (greater than fourfold) important increases in these parameters and a  $>60\%$  increase in the serum half-life ( $p = 0.03$ ) of atorvastatin were observed when coadministered with mibepradil. The half-life of atorvastatin also increased by  $\approx 60\%$  ( $p = 0.052$ ) when coadministered with itraconazole, which elicited a 2.4-fold increase in the  $C_{max}$  of atorvastatin and a 47% increase in the AUC ( $p < 0.001$  for  $C_{max}$  and AUC). Clarithromycin significantly ( $p < 0.001$ ) increased the AUC (and  $C_{max}$ ) of all 3 statins, most markedly simvastatin (~10-fold increase in AUC) and simvastatin acid (12-fold), followed by atorvastatin (greater than fourfold) and then pravastatin (almost twofold). Pravastatin has a neutral drug interaction profile relative to cytochrome P450-3A4 inhibitors, but these substrates markedly increase systemic exposure to simvastatin and atorvastatin. ©2004 by Excerpta Medica, Inc.

Annotator Editor	Annotator Table	$C_{max}$	five-fold	AUC and
Claim				
Drug1	simvastatin	<input type="radio"/> Precipitant	Relationship	substrate of
Drug2		<input checked="" type="radio"/> Enzyme		
<input type="button" value="cancel"/>			<input type="button" value="save"/>	

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7(d) Enter Enzyme (from Column "Value (drop down - for non-quantitative assertions)") and Drug2.



3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are first-line treatments for hypercholesterolemia. Although exceedingly well tolerated, treatment with statins incurs a small risk of myopathy or potentially fatal rhabdomyolysis, particularly when co-administered with medications that increase their systemic exposure. Studies compared the multiple-dose pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with 4 inhibitors of cytochrome P450-3A4 isoenzymes in healthy subjects. Compared with pravastatin alone, co-administration of verapamil, mibepradil, or itraconazole with pravastatin was associated with no significant changes in pravastatin pharmacokinetics. However, concomitant verapamil increased the simvastatin area under the concentration:time curve (AUC) approximately

comparisons  $p < 0.001$ ). Similar (greater than fourfold) important increases in these parameters and a  $>60\%$  increase in the serum half-life ( $p = 0.03$ ) of atorvastatin were observed when coadministered with mibepradil. The half-life of atorvastatin also increased by  $\sim 60\%$  ( $p = 0.052$ ) when coadministered with itraconazole, which elicited a 2.4-fold increase in the  $C_{max}$  of atorvastatin and a 47% increase in the AUC ( $p < 0.001$  for  $C_{max}$  and AUC). Clarithromycin significantly ( $p < 0.001$ ) increased the AUC (and  $C_{max}$ ) of all 3 statins, most markedly simvastatin ( $\sim 10$ -fold increase in AUC) and simvastatin acid (12-fold), followed by atorvastatin (greater than fourfold) and then pravastatin (almost twofold). Pravastatin has a neutral drug interaction profile relative to cytochrome P450-3A4 inhibitors, but these substrates markedly increase systemic exposure to simvastatin and atorvastatin. ©2004 by Excerpta Medica, Inc.

Annotator Editor	Annotator Table	$C_{max}$ five-fold AUC and				
Claim						
Drug1	simvastatin	<input type="radio"/> Precipitant	Relationship	substrate of	<input type="radio"/> Method	clinical trial
Drug2	clarithromycin	<input checked="" type="radio"/> Enzyme	cyp3a4			
<input type="button" value="cancel"/>				<input type="button" value="save"/>		

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7(e) In this case we STILL want to add another claim for the same text span.

This would be indicated when the SAME filename listed in input *Column: Article* has multiple rows, where those rows have the SAME text/location specified in input *Column: The sentence(s) that state the main assertion*.

Therefore, we AGAIN click “add another claim”

(8) Finally, follow the same procedure as in 6(a) to 6(d), as simvastatin-acid again has the “substrate of” relationship.

8(a) We enter Drug 1 (from input *Column Drug*) and Relationship (from input *Column Property*).



Three-hydroxy- $\alpha$ -methylglutaryl coenzyme A reductase inhibitors (statins) are first-line treatments for hypercholesterolemia. Although exceedingly well tolerated, treatment with statins incurs a small risk of myopathy or potentially fatal rhabdomyolysis, particularly when co-administered with medications that increase their systemic exposure. Studies compared the multiple-dose pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with 4 inhibitors of cytochrome P450-3A4 isoenzymes in healthy subjects. Compared with pravastatin alone, co-administration of verapamil, mibepradil, or itraconazole with pravastatin was associated with no significant changes in pravastatin pharmacokinetics. However, concomitant verapamil increased the simvastatin area under the concentration:time curve (AUC) approximately

comparisons  $p < 0.001$ , similar (greater than fourfold) important increases in these parameters and a  $>60\%$  increase in the serum half-life ( $p = 0.03$ ) of atorvastatin were observed when coadministered with mibepradil. The half-life of atorvastatin also increased by  $\sim 60\%$  ( $p = 0.052$ ) when coadministered with itraconazole, which elicited a 2.4-fold increase in the  $C_{max}$  of atorvastatin and a 47% increase in the AUC ( $p < 0.001$  for  $C_{max}$  and AUC). Clarithromycin significantly ( $p < 0.001$ ) increased the AUC (and  $C_{max}$ ) of all 3 statins, most markedly simvastatin ( $\sim 10$ -fold increase in AUC) and simvastatin acid (12-fold), followed by atorvastatin (greater than fourfold) and then pravastatin (almost twofold). Pravastatin has a neutral drug interaction profile relative to cytochrome P450-3A4 inhibitors, but these substrates markedly increase systemic exposure to simvastatin and atorvastatin. ©2004 by Excerpta Medica, Inc.

Annotator Editor	Annotator Table	$C_{max}$	AUC and
------------------	-----------------	-----------	---------

Claim

Drug1	simvastatin-acid	▾	Relationship	substrate of	▾	Method		▾
-------	------------------	---	--------------	--------------	---	--------	--	---

cancel save

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## 8(b) Next we add Method (Clinical Trial).

Three-hydroxy- $\alpha$ -methylglutaryl coenzyme A reductase inhibitors (statins) are first-line treatments for hypercholesterolemia. Although exceedingly well tolerated, treatment with statins incurs a small risk of myopathy or potentially fatal rhabdomyolysis, particularly when co-administered with medications that increase their systemic exposure. Studies compared the multiple-dose pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with 4 inhibitors of cytochrome P450-3A4 isoenzymes in healthy subjects. Compared with pravastatin alone, co-administration of verapamil, mibepradil, or itraconazole with pravastatin was associated with no significant changes in pravastatin pharmacokinetics. However, concomitant verapamil increased the simvastatin area under the concentration:time curve (AUC) approximately

comparisons  $p < 0.001$ , similar (greater than fourfold) important increases in these parameters and a  $>60\%$  increase in the serum half-life ( $p = 0.03$ ) of atorvastatin were observed when coadministered with mibepradil. The half-life of atorvastatin also increased by  $\sim 60\%$  ( $p = 0.052$ ) when coadministered with itraconazole, which elicited a 2.4-fold increase in the  $C_{max}$  of atorvastatin and a 47% increase in the AUC ( $p < 0.001$  for  $C_{max}$  and AUC). Clarithromycin significantly ( $p < 0.001$ ) increased the AUC (and  $C_{max}$ ) of all 3 statins, most markedly simvastatin ( $\sim 10$ -fold increase in AUC) and simvastatin acid (12-fold), followed by atorvastatin (greater than fourfold) and then pravastatin (almost twofold). Pravastatin has a neutral drug interaction profile relative to cytochrome P450-3A4 inhibitors, but these substrates markedly increase systemic exposure to simvastatin and atorvastatin. ©2004 by Excerpta Medica, Inc.

Annotator Editor	Annotator Table	$C_{max}$	AUC and
------------------	-----------------	-----------	---------

Claim

Drug1	simvastatin-acid	▾	<input type="radio"/> Precipitant	Relationship	substrate of	▾	Method	clinical trial	▾
Drug2		▾	<input checked="" type="radio"/> Enzyme		▾				

cancel save

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## 8(c) Once we choose "substrate of" for the relationship, and "clinical trial" for the



Method, we are prompted for the Enzyme as well as for Drug 2.

3-hydroxy- $\beta$ -methylglutaryl coenzyme-A reductase inhibitors (statins) are first-line treatments for hypercholesterolemia. Although exceedingly well tolerated, treatment with statins incurs a small risk of myopathy or potentially fatal rhabdomyolysis, particularly when co-administered with medications that increase their systemic exposure. Studies compared the multiple-dose pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with 4 inhibitors of cytochrome P450-3A4 isoenzymes in healthy subjects. Compared with pravastatin alone, co-administration of verapamil, mibepradil, or itraconazole with pravastatin was associated with no significant changes in pravastatin pharmacokinetics. However, concomitant verapamil increased the simvastatin area under the concentration:time curve (AUC) approximately

comparisons  $p < 0.001$ ). Similar (greater than fourfold) important increases in these parameters and a >60% increase in the serum half-life ( $p = 0.03$ ) of atorvastatin were observed when coadministered with mibepradil. The half-life of atorvastatin also increased by >60% ( $p = 0.052$ ) when coadministered with itraconazole, which elicited a 2.4-fold increase in the  $C_{max}$  of atorvastatin and a 47% increase in the AUC ( $p < 0.001$  for  $C_{max}$  and AUC). Clarithromycin significantly ( $p < 0.001$ ) increased the AUC (and  $C_{max}$ ) of all 3 statins, most markedly simvastatin (~10-fold increase in AUC) and simvastatin acid (12-fold), followed by atorvastatin (greater than fourfold) and then pravastatin (almost twofold). Pravastatin has a neutral drug interaction profile relative to cytochrome P450-3A4 inhibitors, but these substrates markedly increase systemic exposure to simvastatin and atorvastatin. ©2004 by Excerpta Medica, Inc.

Annotator Editor	Annotator Table	$C_{max}$ five-fold AUC and						
Claim								
Drug1	simvastatin-acid	<input type="radio"/> Precipitant	Relationship	substrate of	<input type="button" value="▼"/>	Method	clinical trial	<input type="button" value="▼"/>
Drug2	clarithromycin	<input checked="" type="radio"/> Enzyme		cyp3a4	<input type="button" value="▼"/>			
<input type="button" value="cancel"/>				<input type="button" value="save"/>				

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8(e) Once all claims are entered, click “finish with this span, move on”



Three-hydroxy- $\beta$ -methylglutaryl coenzyme-A reductase inhibitors (statins) are first-line treatments for hypercholesterolemia. Although exceedingly well tolerated, treatment with statins incurs a small risk of myopathy or potentially fatal rhabdomyolysis, particularly when co-administered with medications that increase their systemic exposure. Studies compared the multiple-dose pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with 4 inhibitors of cytochrome P450-3A4 isoenzymes in healthy subjects. Compared with pravastatin alone, co-administration of verapamil, mibepradil, or itraconazole with pravastatin was associated with no significant changes in pravastatin pharmacokinetics. However, concomitant verapamil increased the simvastatin area under the concentration:time curve (AUC) approximately

comparisons  $p < 0.001$ ). Similar (greater than fourfold) important increases in these parameters and a >60% increase in the serum half-life ( $p = 0.03$ ) of atorvastatin were observed when coadministered with mibepradil. The half-life of atorvastatin also increased by ≈60% ( $p = 0.052$ ) when coadministered with itraconazole, which elicited a 2.4-fold increase in the  $C_{max}$  of atorvastatin and a 47% increase in the AUC ( $p < 0.001$  for  $C_{max}$  and AUC). Clarithromycin significantly ( $p < 0.001$ ) increased the AUC (and  $C_{max}$ ) of all 3 statins, most markedly simvastatin (~10-fold increase in AUC) and simvastatin acid (12-fold), followed by atorvastatin (greater than fourfold) and then pravastatin (almost twofold). Prava-

interaction profile relative to  
inhibitors, but these substrates  
exposure to simvastatin and  
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Annotator Editor		An	Add data to the same text span for claim clarithromycin interacts with atorvastatin	OK	
			Add another claim to the same text span	OK	
			Move to a different text span (finish)	OK	clinical trial
					save
<input type="button" value="cancel"/>					

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- (9) This takes you to the “Annotator Table”. This specifies the information that is desired. You will annotate a span of the document and add text, for whatever information is available in the document.

Three-hydroxy- $\beta$ -methylglutaryl coenzyme-A reductase inhibitors (statins) are first-line treatments for hypercholesterolemia. Although exceedingly well tolerated, treatment with statins incurs a small risk of myopathy or potentially fatal rhabdomyolysis, particularly when co-administered with medications that increase their systemic exposure. Studies compared the multiple-dose pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with 4 inhibitors of cytochrome P450-3A4 isoenzymes in healthy subjects. Compared with pravastatin alone, co-administration of verapamil, mibepradil, or itraconazole with pravastatin was associated with no significant changes in pravastatin pharmacokinetics. However, concomitant verapamil increased the simvastatin area under the concentration:time curve (AUC) approximately

comparisons  $p < 0.001$ ). Similar (greater than fourfold) important increases in these parameters and a >60% increase in the serum half-life ( $p = 0.03$ ) of atorvastatin were observed when coadministered with mibepradil. The half-life of atorvastatin also increased by ≈60% ( $p = 0.052$ ) when coadministered with itraconazole, which elicited a 2.4-fold increase in the  $C_{max}$  of atorvastatin and a 47% increase in the AUC ( $p < 0.001$  for  $C_{max}$  and AUC). Clarithromycin significantly ( $p < 0.001$ ) increased the AUC (and  $C_{max}$ ) of all 3 statins, most markedly simvastatin (~10-fold increase in AUC) and simvastatin acid (12-fold), followed by atorvastatin (greater than fourfold) and then pravastatin (almost twofold). Pravastatin has a neutral drug interaction profile relative to cytochrome P450-3A4 inhibitors, but these substrates markedly increase systemic exposure to simvastatin and atorvastatin. ©2004 by Excerpta Medica, Inc.

Annotator Editor		Annotator Table		five and		Material / Data				
Claim		Material / Data								
simvastatin substrate of cyp3a4							<input type="button" value="+ add new row for material/data"/>			
Method	clinical trial	Ev-Relationship	Participants	Atorvastatin Dose	Clarithromycin Dose(P)	AUC Ratio	Clearance Ratio	Cmax Ratio	Half-life Ratio	Randomization
<input type="button" value="edit claim"/>	<input type="button" value="view claim span"/>									

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**Note that the claim shown is the last claim entered. But you can work on the claims in any order.**

**Note: if you click on a data cell without having a text span highlighted, you will get the message "please select a span before you add any materials/data".**

Three-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (statins) are first-line treatments for hypercholesterolemia. Although exceedingly well tolerated, treatment with statins incurs a small risk of myopathy or potentially fatal rhabdomyolysis, particularly when co-administered with medications that increase their systemic exposure. Studies compared the multiple-dose pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with 4 inhibitors of cytochrome P450-3A4 isoenzymes in healthy subjects. Compared with pravastatin alone, co-administration of verapamil, mibepradil, or itraconazole with pravastatin was associated with no significant changes in pravastatin pharmacokinetics. However,

comparisons  $p < 0.001$ ). Similar (greater than fourfold) important increases in these parameters and a  $>60\%$  increase in the serum half-life ( $p = 0.03$ ) of atorvastatin were observed when coadministered with mibepradil. The half-life of atorvastatin also increased by  $\approx 60\%$  ( $p = 0.052$ ) when coadministered with itraconazole, which elicited a 2.4-fold increase in the  $C_{max}$  of atorvastatin and a 47% increase in the AUC ( $p < 0.001$  for  $C_{max}$  and AUC). Clarithromycin significantly ( $p < 0.001$ ) increased the AUC (and  $C_{max}$ ) of all 3 statins, most markedly simvastatin ( $\sim 10$ -fold increase in AUC) and simvastatin acid (12-fold), followed by atorvastatin (greater than fourfold) and then pravastatin (almost twofold). Prava-

Annotator Editor			
		Claim	
simvastatin substrate of cyp3a4		Please select a span before you add any material/data!	
Method	clinical trial	Half-life	Randomization
<input type="button" value="edit claim"/>	<input type="button" value="view claim s"/>		
		<input type="button" value="New row for material/data"/>	

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(10) Now we are ready to add the information associated with one claim, in the “material/data” part of the table.

10(a) First, determine which claim (row of the input document) you will work on.

10(b) Next, gather the required information from the input document, as follows:

- a. Dosage/administration information for drugs specified in the claim above. Typically, Skim near the methods [*Column: The sentence(s), table(s), and/or figure(s) that specify the methods*]
- b. Relationship – *Column: Property*
- c. Method type – *Clinical Trial*
- d. Drug2/inhibitor – *Column: Value (drop down - for non-quantitative assertions)*



- e. Participants - *Column: The sentence(s), table(s), and/or figure(s) that specify the methods and Column: The sentence(s), table(s), and/or figure(s) that specify the results*
- f. AUC Ratio, Cmax Ratio, Clearance Ratio, and/or Half-life (T1/2) Ratio - *Column: The sentence(s), table(s), and/or figure(s) that specify the results*
- g. Ev\_relationship (evidence relationship) - *Column: This is evidence. If it's an "against", then selects "refuse", otherwise selects "support".*

10(c) Select the text span associated with a data item and click the MP button. Here we select the text associated with the object drug dosage and administration. Read through, select clinical trial for methods.

10(d) Roll over “add material/data for”, and choose the claim you would like to add data for.

June 2001.<sup>1</sup> Statin-associated myopathy is a dose-related phenomenon: its incidence increases about fivefold (from ~0.3% to ~1.5%) when certain statins (e.g., lovastatin, simvastatin, or atorvastatin) are coadministered with medications that share their metabolic pathways and/or increase their systemic exposure.<sup>2,3</sup> These include lipid-lowering agents such as fibrates<sup>4</sup> (especially gemfibrozil), calcium channel blockers,<sup>5–8</sup> immunosuppressive agents (e.g., cyclosporine),<sup>9,10</sup> macrolide antibiotics (e.g., clarithromycin),<sup>11,12</sup> imidazole antifungal agents (e.g.,itraconazole),<sup>13–16</sup> protease inhibitors for human immunodeficiency virus,<sup>17</sup> and combinations of these and other drugs,<sup>18–21</sup> including over-the-counter agents

From the Office of Health Promotion and Disease Prevention, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia. This study was supported by Bristol-Myers Squibb Co., Princeton, New Jersey. Manuscript received February 9, 2001; re-

## METHODS

**Overview of study designs:** This report summarizes data from 4 small, short-term parallel-group studies that evaluated the effects of CYP3A4 inhibitors on the multiple-dose pharmacokinetics of statins in 4 groups of healthy subjects. These studies, which were conducted from January 6, 1998 through April 4, 1998, evaluated the pharmacokinetics of (1) 40 mg of pravastatin or 40 mg of simvastatin when coadministered with 480 mg of extended-release verapamil; (2) 40 mg of pravastatin or 80 mg of atorvastatin when coadministered with 100 mg of clarithromycin twice daily; (3) 40 mg of pravastatin or 80 mg of simvastatin when coadministered with 200 mg of diltiazem; and (4) 40 mg of pravastatin or 80 mg of simvastatin when coadministered with 200 mg of ketoconazole.

create a claim

add material/data for

clarithromycin interacts with atorvastatin  
clarithromycin interacts with pravastatin  
simvastatin substrate of cy3a4  
simvastatin-acid substrate of cy3a4

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10(f) The annotator table appears, and the highlighted text has been selected. The highlighted text will get associated with the data cell you click, for the claim and method shown on the left.



June 2001.<sup>1</sup> Statin-associated myopathy is a dose-related phenomenon: its incidence increases about fivefold (from ~0.3% to ~1.5%) when certain statins (e.g., lovastatin, simvastatin, or atorvastatin) are coadministered with medications that share their metabolic pathways and/or increase their systemic exposure.<sup>2,3</sup> These include lipid-lowering agents such as fibrates<sup>4</sup> (especially gemfibrozil), calcium channel blockers,<sup>5–8</sup> immunosuppressive agents (e.g., cyclosporine),<sup>9,10</sup> macrolide antibiotics (e.g., clarithromycin),<sup>11,12</sup> imidazole antifungal agents (e.g., itraconazole),<sup>13–16</sup> protease inhibitors for human immunodeficiency virus,<sup>17</sup> and combinations of these and other drugs,<sup>18–21</sup> including over-the-counter agents

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Annotator Editor		Annotator Table	
<b>Claim</b>		<b>Material / Data</b>	
clarithromycin interacts with atorvastatin   ▾		+ add new row for material/data	
Method	clinical trial   ▾	Ev-Relationship	Participants
edit claim		Atorvastatin Dose	Clarithromycin Dose(P)
view claim span		AUC Ratio	Clearance Ratio
		Cmax Ratio	Half-life Ratio
			Randomization

10(g) Now click on any cell in the data table associated the highlighted text. In this case we first click on the cell labeled "Atorvastatin Dose".

10(h) Enter the dose as text (in mg). Choose the formulation from the drop down. In this case the duration (days) is not specified in the text, so we leave it blank. Choose the regimen from the drop down.

**Note: For each material/data form, all the fields have to be filled out! Otherwise, the data won't be saved.**

June 2001.<sup>1</sup> Statin-associated myopathy is a dose-related phenomenon: its incidence increases about fivefold (from ~0.3% to ~1.5%) when certain statins (e.g., lovastatin, simvastatin, or atorvastatin) are coadministered with medications that share their metabolic pathways and/or increase their systemic exposure.<sup>2,3</sup> These include lipid-lowering agents such as fibrates<sup>4</sup> (especially gemfibrozil), calcium channel blockers,<sup>5–8</sup> immunosuppressive agents (e.g., cyclosporine),<sup>9,10</sup> macrolide antibiotics (e.g., clarithromycin),<sup>11,12</sup> imidazole antifungal agents (e.g., itraconazole),<sup>13–16</sup> protease inhibitors for human immunodeficiency virus,<sup>17</sup> and combinations of these and other drugs,<sup>18–21</sup> including over-the-counter agents

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Annotator Editor		Annotator Table	
<b>Material / Data</b>		clarithromycin interacts with atorvastatin	
Ev-Relationship	Participants	Object Dose	Precipitant Dose
Atorvastatin Dose	80 mg	Formulation	oral   ▾
Duration(days)		Cmax	
		Half-life	
		Randomization	
cancel		delete	
save		save and close	

**NOTE:** Formulation

If the highlighted text does not specifically indicate that it's an oral dose (such as tablet, pill, etc), assume that the authors mean oral and select oral. If the authors specifically refer to an IV or the dose as mg/mL over time, then select IV.

10(i) Click "save". This allows you to add additional information associated with the same highlighted text span and the same claim. 10(a) In this case, the highlighted text span is also associated with the precipitant dose, so we next click "precipitant dose".

10(j) Fill in the precipitant dose (the top right corner shows the drugs, in case we need to know which drug the precipitant is). Choose the formulation from the drop down. Choose the regimen from the drop down. In this case the duration (days) is not specified in the text, so we leave it blank.

June 2001.<sup>1</sup> Statin-associated myopathy is a dose-related phenomenon: its incidence increases about fivefold (from ~0.3% to ~1.5%) when certain statins (e.g., lovastatin, simvastatin, or atorvastatin) are coadministered with medications that share their metabolic pathways and/or increase their systemic exposure.<sup>2,3</sup> These include lipid-lowering agents such as fibrates<sup>4</sup> (especially gemfibrozil), calcium channel blockers,<sup>5–8</sup> immunosuppressive agents (e.g., cyclosporine),<sup>9,10</sup> macrolide antibiotics (e.g., clarithromycin),<sup>11,12</sup> imidazole antifungal agents (e.g., itraconazole),<sup>13–16</sup> protease inhibitors for human immunodeficiency virus,<sup>17</sup> and combinations of these and other drugs,<sup>18–21</sup> including over-the-counter agents

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**METHODS**

**Overview of study designs:** This report summarizes data from 4 small, short-term parallel-group studies that evaluated the effects of CYP3A4 inhibitors on the multiple-dose pharmacokinetics of statins in 4 groups of healthy subjects. These studies, which were conducted from January 6, 1998 through April 4, 1998, evaluated the pharmacokinetics of (1) 40 mg of pravastatin or 40 mg of simvastatin when coadministered with 480 mg of extended-release verapamil; (2) 40 mg of pravastatin or 80 mg of atorvastatin when coadministered with 100 mg of mibepradil; (3) 40 mg of pravastatin or 80 mg of atorvastatin when coadministered with 200 mg of itraconazole; and (4) 40 mg of pravastatin, 40 mg of simvastatin, or 80 mg of atorvastatin when coadministered with 500 mg of clarithromycin twice daily.

Annotator Editor		Annotator Table		Material / Data									
				clarithromycin interacts with atorvastatin									
Ev-Relationship	Participants	Object Dose	Precipitant Dose	AUC	Clearance	Cmax	Half-life	Randomization					
Clarithromycin Dose	500 mg	Formulation	oral	▾	Duration(days)		Regimen	BID	▾				
cancel				delete				save				save and close	

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**NOTE:** Formulation

If the highlighted text does not specifically indicate that it's an oral dose (such as tablet, pill, etc), assume that the authors mean oral and select oral. If the authors specifically refer to an IV or the dose as mg/mL over time, then select IV.

10(k) Click "save and close".



10(l) You then get back to table view.

June 2001. Statin-associated myopathy is a dose related phenomenon: its incidence increases about fivefold (from ~0.3% to ~1.5%) when certain statins (e.g., lovastatin, simvastatin, or atorvastatin) are coadministered with medications that share their metabolic pathways and/or increase their systemic exposure.<sup>2,3</sup> These include lipid-lowering agents such as fibrates<sup>4</sup> (especially gemfibrozil), calcium channel blockers,<sup>5–8</sup> immunosuppressive agents (e.g., cyclosporine),<sup>9,10</sup> macrolide antibiotics (e.g., clarithromycin),<sup>11,12</sup> imidazole antifungal agents (e.g., itraconazole),<sup>13–16</sup> protease inhibitors for human immunodeficiency virus,<sup>17</sup> and combinations of these and other drugs,<sup>18–21</sup> including over-the-counter agents

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Annotator Editor		Annotator Table		Material / Data							
Claim		Material / Data									
		<a href="#">+ add new row for material/data</a>									
Method	clinical trial	Ev-Relationship	Participants	Atorvastatin Dose	Clarithromycin Dose(P)	AUC Ratio	Clearance Ratio	Cmax Ratio	Half-life Ratio	Randomization	
<a href="#">edit claim</a>	<a href="#">view claim span</a>	1		80	500						

11(a) Next we select the text associated with the participants.

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Pharmacokinetic effects of clarithromycin on pravastatin, atorvastatin, and simvastatin  
 This randomized, open-label, parallel-group study evaluated the effects of co-clarithromycin on the multiple-dose pharmacokinetics of pravastatin, simvastatin, and atorvastatin. Forty-five healthy men and women were randomly assigned to open-label administration of 40 mg of pravastatin ( $n = 15$ ), 40 mg of simvastatin ( $n = 15$ ), or 80 mg of atorvastatin ( $n = 15$ ). In each group, the statin was administered once daily after breakfast on study days 1 to 7 and days 10 to 17. All subjects also received 500 mg of clarithromycin twice daily (morning and evening) on days 10 to 18. Blood samples for pharmacokinetic analysis were obtained on days 7 and 17.

11(b) Click MP.11 (c) Roll over “add material/data for”, and choose the claim you would like to add data for.



## Pharmacokinetic effects of clarithromycin on pravastatin, atorvastatin, and simvastatin

This randomized, open-label, parallel-group study evaluated the effects of clarithromycin on the multiple-dose pharmacokinetics of pravastatin, simvastatin, and atorvastatin. Forty-five healthy men and women were randomly assigned to open-label administration of 40 mg of pravastatin ( $n = 15$ ), 40 mg of simvastatin ( $n = 15$ ), or 80 mg of atorvastatin ( $n = 15$ ). In each group, the statin was administered once daily after breakfast on study days 1 to 7 and days 10 to 17. All subjects also received 500 mg of clarithromycin twice daily (morning and evening) on days 10 to 18. Blood samples for pharmacokinetic analysis were obtained on days 7 and 17.

[create a claim](#)  
[add material/data for](#)

clarithromycin interacts with atorvastatin  
 clarithromycin interacts with pravastatin  
 simvastatin substrate of cy3a4  
 simvastatin-acid substrate of cy3a4

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11(d) Click the participants cell in table view.

11(e) Fill in the number of study participants.

## Pharmacokinetic effects of clarithromycin on pravastatin, atorvastatin, and simvastatin

This randomized, open-label, parallel-group study evaluated the effects of concomitant clarithromycin on the multiple-dose pharmacokinetics of pravastatin, simvastatin, and atorvastatin. Forty-five healthy men and women were randomly assigned to open-label administration of 40 mg of pravastatin ( $n = 15$ ), 40 mg of simvastatin ( $n = 15$ ), or 80 mg of atorvastatin ( $n = 15$ ). In each group, the statin was administered once daily after breakfast on study days 1 to 7 and days 10 to 17. All subjects also received 500 mg of clarithromycin twice daily (morning and evening) on days 10 to 18. Blood samples for pharmacokinetic analysis were obtained on days 7 and 17.

Annotator Editor		Annotator Table		Material / Data						clarithromycin interacts with atorvastatin	
Ev_relationship	Participants	Object Dose	Precipitant Dose	AUC	Clearance	Cmax	Half-life	Randomization			
The number of study participants <input type="text" value="45"/>											
<input type="button" value="cancel"/> <input type="button" value="delete"/>				<input type="button" value="save"/> <input type="button" value="save and close"/>							

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11(f) Click “save and close” to be taken back to the annotator table.

Pharmacokinetic effects of clarithromycin on pravastatin, atorvastatin, and simvastatin

This randomized, open-label, parallel-group study evaluated the effects of concomitant clarithromycin on the multiple-dose pharmacokinetics of pravastatin, simvastatin, and atorvastatin. Forty-five healthy men and women were randomly assigned to open-label administration of 40 mg of pravastatin ( $n = 15$ ), 40 mg of simvastatin ( $n = 15$ ), or 80 mg of atorvastatin ( $n = 15$ ). In each group, the statin was administered once daily after breakfast on study days 1 to 7 and days 10 to 17. All subjects also received 500 mg of clarithromycin twice daily (morning and evening) on days 10 to 18. Blood samples for pharmacokinetic analysis were obtained on days 7 and 17.

Annotator Editor		Annotator Table		Material / Data						
Claim		Material / Data								
clarithromycin interacts with atorvastatin ▾		+ add new row for material/data								
Method	clinical trial ▾	Ev-Relationship	Participants	Atorvastatin Dose	Clarithromycin Dose(P)	AUC Ratio	Clearance Ratio	Cmax Ratio	Half-life Ratio	Randomization
edit claim	view claim span	1		80	500					

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(12) Next we will work on the AUC Ratio.

### **NOTE: AUC**

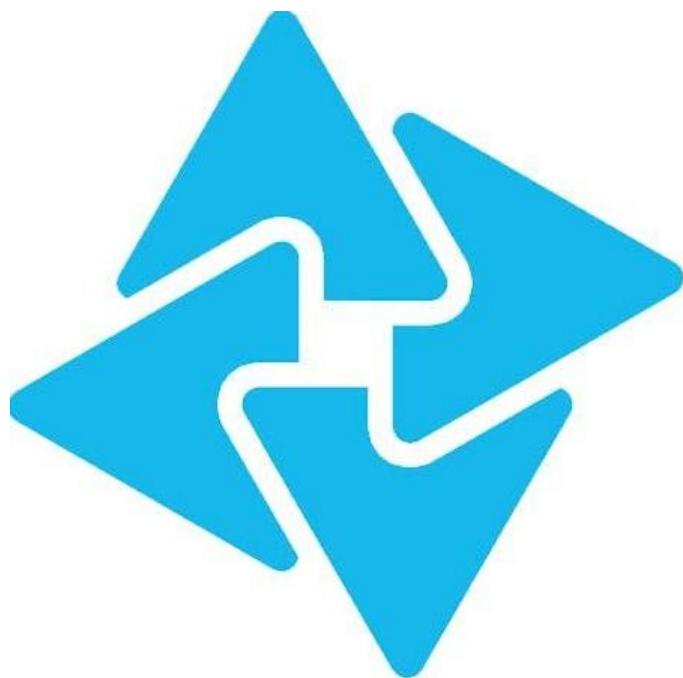
AUC is a measurement of the total drug exposure over time. **The focus is on the altered AUC values.** An increase in AUC means an increase in drug exposure; a decrease means a decrease in drug exposure. If the statement includes information about the AUC (which will always refer to the object drug), in the AUC Ratio fields, type the AUC Ratio value in the AUC Ratio: text box, the AUC Ratio type (percent, fold, unk), and direction (increase, decrease, unk). If the AUC Ratio is not mentioned at all, select or type unk in all fields. Sometimes, statements will refer only to exposure, not AUC Ratio directly. In those cases, assume they mean AUC Ratio, and annotate accordingly.

#### **Examples of AUC information include:**

- “Cyclosporine AUC and Cmax were determined before and after the administration of fluconazole 200 mg daily for 14 days in eight renal transplant patients who had been on cyclosporine therapy for at least 6 months and on a stable cyclosporine dose for at least 6 weeks.”
- “Concomitant treatment with rabeprazole (20 mg daily) and ketoconazole in healthy subjects decreased the bioavailability of ketoconazole by 30% and increased the AUC and Cmax for digoxin by 19% and 29%, respectively. Therefore, patients may need to be monitored when such drugs are taken



concomitantly with rabeprazole. Co-administration of rabeprazole and antacids produced no clinically relevant changes in plasma rabeprazole concentrations."





12(a) Highlight the “AUC Ratio” information.

12(b) Click MP

12(c) Roll over “add material/data for”, and choose the claim you would like to add data for.

<b>TABLE 4</b> Pharmacokinetic Effects of Clarithromycin on Pravastatin, Simvastatin, and Atorvastatin					
Statin	Parameter	Statin Alone	Statin + Clarithromycin	%Change	p Value
Pravastatin, 40 mg	C <sub>max</sub> (ng/ml)	18	41	+128	<0.001
	AUC (ng/ml/h)	54	114	+110	<0.001
Simvastatin, 40 mg	C <sub>max</sub> (ng/ml)	7	50	+609	<0.001
	AUC (ng/ml/h)	22	219	+885	<0.001
Simvastatin acid	C <sub>max</sub> (ng/ml)	1	10	+677	<0.001
	AUC (ng/ml/h)	6	73	+1,092	<0.001
Atorvastatin, 80 mg	C <sub>max</sub> (ng/ml)	21	113	+446	<0.001
	AUC (ng/ml/h)	102	454	+343	<0.001

Data are geometric means.

simvastatin, and atorvastatin suggest that the non-CYP substrate pravastatin is the statin least susceptible to pharmacokinetic interactions with CYP3A4 inhibitors. Although rare, rhabdomyolysis with statins remains an important and timely issue. Recently, the manufacturer of rosuvastatin wrote to United Kingdom and

clarithromycin interacts with atorvastatin

clarithromycin interacts with pravastatin

simvastatin substrate of cy3a4

simvastatin-acid substrate of cy3a4

should be

Rosuvastatin is an inhibitor of CYP2C9 and CYP2C19 that interacts chiefly with cyclosporine, warfarin, and gemfibrozil but not with fenofibrate, azole antifungals, or

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12(d) Click the “AUC Ratio” cell in the table.

<b>TABLE 4</b> Pharmacokinetic Effects of Clarithromycin on Pravastatin, Simvastatin, and Atorvastatin					
Statin	Parameter	Statin Alone	Statin + Clarithromycin	%Change	p Value
Pravastatin, 40 mg	C <sub>max</sub> (ng/ml)	18	41	+128	<0.001
	AUC (ng/ml/h)	54	114	+110	<0.001
Simvastatin, 40 mg	C <sub>max</sub> (ng/ml)	7	50	+609	<0.001
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Rosuvastatin is an inhibitor of CYP2C9 and CYP2C19 that interacts chiefly with cyclosporine, warfarin, and gemfibrozil but not with fenofibrate, azole antifungals, or

Annotator Editor		Annotator Table		Material / Data						
Claim		Material / Data								
clarithromycin interacts with atorvastatin ▾		+ add new row for material/data								
Method	clinical trial ▾	Ev-Relationship	Participants	Atorvastatin Dose	Clarithromycin Dose(P)	AUC Ratio	Clearance Ratio	Gmax Ratio	Half-life Ratio	Randomization
edit claim	view claim span	1	45	80	500					

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12(e) Here we type in the numerical portion of the “% Change” (343) into “AUC Ratio”, select the radio button “percent” and the AUC Ratio direction “increase”.

<b>TABLE 4</b> Pharmacokinetic Effects of Clarithromycin on Pravastatin, Simvastatin, and Atorvastatin					
Statin	Parameter	Statin Alone	Statin + Clarithromycin	%Change	p Value
Pravastatin, 40 mg	$C_{max}$ (ng/ml)	18	41	+128	<0.001
	AUC (ng/ml/h)	54	114	+110	<0.001
Simvastatin, 40 mg	$C_{max}$ (ng/ml)	7	50	+609	<0.001
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Atorvastatin, 80 mg	$C_{max}$ (ng/ml)	21	113	+446	<0.001
	AUC (ng/ml/h)	102	454	+343	<0.001

Data are geometric means.

Annotator Editor
Annotator Table

**Material / Data**

Ev\_relationship Participants Object Dose Precipitant Dose **AUC** Clearance Cmax Half-life Randomization

**AUC Ratio**   unchanged    **AUC Type**  unk  percent  fold    **AUC Direction**  unk  increase  decrease

12(f) When we click “save and close” the AUC Ratio appears in the table.

<b>TABLE 4</b> Pharmacokinetic Effects of Clarithromycin on Pravastatin, Simvastatin, and Atorvastatin					
Statin	Parameter	Statin Alone	Statin + Clarithromycin	%Change	p Value
Pravastatin, 40 mg	$C_{max}$ (ng/ml)	18	41	+128	<0.001
	AUC (ng/ml/h)	54	114	+110	<0.001
Simvastatin, 40 mg	$C_{max}$ (ng/ml)	7	50	+609	<0.001
	AUC (ng/ml/h)	22	219	+885	<0.001
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Atorvastatin, 80 mg	$C_{max}$ (ng/ml)	21	113	+446	<0.001
	AUC (ng/ml/h)	102	454	+343	<0.001

Data are geometric means.

Annotator Editor
Annotator Table

**Claim**

clarithromycin interacts with atorvastatin

Method	clinical trial	Participants	Num who Complete	Atorvastatin Dose	Clarithromycin Dose(P)	AUC Ratio	Clearance Ratio	Cmax Ratio	Half-life Ratio	Randomization
<input type="button" value="edit claim"/>	<input type="button" value="view claim span"/>	1	45		80	500	343			

(13) Next we work on the Cmax Ratio.



**NOTE: Cmax** is a measurement of the highest serum concentration of the drug in the blood after administration of one dose. **The focus is on the altered Cmax values.** If the statement includes information about Cmax Ratio (which will always refer to the object drug), in the Cmax Ratio fields capture the Cmax Ratio value, the Cmax Ratio type (percent, fold, unk), and Cmax Ratio direction (increase, decrease, unk) or else type/select unk in all fields accordingly.

### Examples of Cmax information include:

- “Concomitant treatment with rabeprazole (20 mg daily) and ketoconazole in healthy subjects decreased the bioavailability of ketoconazole by 30% and increased the AUC and Cmax for digoxin by 19% and 29%, respectively. Therefore, patients may need to be monitored when such drugs are taken concomitantly with rabeprazole. Co-administration of rabeprazole and antacids produced no clinically relevant changes in plasma rabeprazole concentrations.”
- “There was an increase in mean repaglinide Cmax and AUC (1.7- and 2.4-fold, respectively), following repeated doses of teriflunomide and a single dose of 0.25 mg repaglinide, suggesting that teriflunomide is an inhibitor of CYP2C8 in vivo. The magnitude of interaction could be higher at the recommended repaglinide dose [see DRUG INTERACTIONS (7)].”

13(a) Next highlight the “Cmax Ratio” information.

TABLE 4 Pharmacokinetic Effects of Clarithromycin on Pravastatin, Simvastatin, and Atorvastatin						
Statin	Parameter	Statin Alone	Statin + Clarithromycin	%Change	p Value	
Pravastatin, 40 mg	C <sub>max</sub> (ng/ml)	18	41	+128	<0.001	
	AUC (ng/ml/h)	54	114	+110	<0.001	
Simvastatin, 40 mg	C <sub>max</sub> (ng/ml)	7	50	+609	<0.001	
	AUC (ng/ml/h)	22	219	+885	<0.001	
Simvastatin acid	C <sub>max</sub> (ng/ml)	1	10	+677	<0.001	
	AUC (ng/ml/h)	6	73	+1,092	<0.001	
Atorvastatin, 80 mg	C <sub>max</sub> (ng/ml)	21	113	+446	<0.001	
	AUC (ng/ml/h)	102	454	+343	<0.001	

Data are geometric means.

that the non-CYP substrate pravastatin is the statin least susceptible to pharmacokinetic interactions with CYP3A4 inhibitors. Although rare, rhabdomyolysis with statins remains an important and timely issue. Recently, the manufacturer of rosuvastatin wrote to United Kingdom and

n prescribers to remind them starting dose of rosuvastatin should be 10 mg.

Rosuvastatin is an inhibitor of CYP2C9 and CYP2C19 that interacts chiefly with clopidogrel.

13(b) Click MP



13(c) Roll over “add material/data for”, and choose the claim you would like to add data for.

<b>TABLE 4</b> Pharmacokinetic Effects of Clarithromycin on Pravastatin, Simvastatin, and Atorvastatin						
Statin	Parameter	Statin Alone	Statin + Clarithromycin	%Change	p Value	
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clarithromycin interacts with atorvastatin  
clarithromycin interacts with pravastatin  
simvastatin substrate of cy3a4  
simvastatin-acid substrate of cy3a4

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13(d) The table appears, select “Cmax Ratio”.

13(e) Here we use the “%Change” to specify the “Cmax Ratio”, select the radio button “percent” and the Cmax Ratio direction “increase”.

<b>TABLE 4</b> Pharmacokinetic Effects of Clarithromycin on Pravastatin, Simvastatin, and Atorvastatin						
Statin	Parameter	Statin Alone	Statin + Clarithromycin	%Change	p Value	
Pravastatin, 40 mg	$C_{max}$ (ng/ml)	18	41	+128	<0.001	
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Data are geometric means.

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Rosuvastatin is an inhibitor of CYP2C9 and CYP2C19 that interacts chiefly with cyclosporine. war-

Annotator Editor
Annotator Table

Material / Data							
<input type="checkbox"/> Ev_relationship	<input type="checkbox"/> Participants	<input type="checkbox"/> Object Dose	<input type="checkbox"/> Precipitant Dose	<input type="checkbox"/> AUC	<input type="checkbox"/> Clearance	<input checked="" type="checkbox"/> Cmax	<input type="checkbox"/> Half-life

Cmax Ratio 
 unchanged
Cmax Type  unk  percent  fold
Cmax Direction  unk  increase  decrease

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13(f) Click “save and close” to be taken back to the annotator table.

(14) Verify that all the information that was available appears in the table.

<b>TABLE 4</b> Pharmacokinetic Effects of Clarithromycin on Pravastatin, Simvastatin, and Atorvastatin						
Statin	Parameter	Statin Alone	Statin + Clarithromycin	%Change	p Value	
Pravastatin, 40 mg	C <sub>max</sub> (ng/ml)	18	41	+128	<0.001	
	AUC (ng·ml/h)	54	114	+110	<0.001	
Simvastatin, 40 mg	C <sub>max</sub> (ng/ml)	7	50	+609	<0.001	
	AUC (ng·ml/h)	22	219	+885	<0.001	
Simvastatin acid	C <sub>max</sub> (ng/ml)	1	10	+677	<0.001	
	AUC (ng·ml/h)	6	73	+1,092	<0.001	
Atorvastatin, 80 mg	C <sub>max</sub> (ng/ml)	21	113	+446	<0.001	
	AUC (ng·ml/h)	102	454	+343	<0.001	

Data are geometric means.

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Annotator Editor		Annotator Table		Material / Data						
Claim		Material / Data								
clarithromycin interacts with atorvastatin		<input type="button" value="+ add new row for material/data"/>								
Method	clinical trial	Participants	Num who Complete	Atorvastatin Dose	Clarithromycin Dose(P)	AUC Ratio	Clearance Ratio	Cmax Ratio	Half-life Ratio	Randomization
<input type="button" value="edit claim"/> <input type="button" value="view claim span"/>		1	45		80	500	343		446	

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(15) Repeat the same process (from steps 13 to 14) for Clearance ratio, half-life ratio and randomization data/material fields for the same claim.

(16) Repeat the same process (from steps 8 to 14) for each of the remaining claims associated with this paper. Each claim is associated with a row of the input file.

(17) If you do as above, the annotations will be saved in the system safely. Please remember to log off NoMachine and Pulse Secure every time you finish the work.

#### Version History

S.N o	Date	Version	Changes Description
1	10-Feb-16	V1	Creation
2	26-May-16	V2	Add authors, fix spelling of Pittsburgh, add mockups of new annotation interface. Finalized screenshots for v2.
3	21-July-16	V3	Add evidence relationship. Finalized the material/data form.
4	09-August-16	V4	Add Vlan Information, URL. Add Ratio and remove PK.