Performing Safety Review with Empirica Study

Oracle® Health Sciences

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1 Introduction

1.1 What Is Empirica Study?

Empirica Study, developed by Oracle, is a Web-based application designed for use by clinical safety scientists and others who monitor and analyze the safety of products in clinical studies. Empirica Study provides the following:

- Support of safety analysis and review of clinical trials data
- Statistical and procedural approaches outlined in recent FDA guidance on safety review and risk management
- Extensive use of graphical presentations that make data meaningful
- Easy access to a full range of clinical data
- Data exploration and hypothesis generation
- A combination of familiar statistical techniques with innovative methods for the detection of syndromes and evaluation of potential signals

Within Empirica Study, the features accessed from the Safety Review tab are designed specifically to meet the needs of the users who are responsible for performing drug safety review according to the *Reviewer Guidance on Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review* (prepared by the Integrated Summary of Safety group, a subcommittee of Good Review Practices). Empirica Study safety review features are intended to facilitate reviews that are systematic, efficient, consistent, and timely.

By clicking the Safety Review tab you can view a variety of tables and graphs providing counts and percentages of subjects who received the treatment drug and comparator drug and experienced particular events or tests. For example, you can view a disposition summary for the study, the cumulative incidence of adverse events over time, or lab test result changes from baseline. You can opt to review the study population by characteristics such as sex, race, and age.

The Safety Review tab also provides access to the results of screening analysis, which include statistically computed “scores” to help you evaluate the relationships between adverse events or test results and the study drug.

This guide is intended to introduce the features that you can access from the Safety Review tab. For information about other features in Empirica Study, see the online help.

1.2 Logging In

To log in to Empirica Study:

1. Using Microsoft® Internet Explorer, go to the Web address provided by your administrator. The application portal page appears.

2. Optionally bookmark the application portal page in Internet Explorer, so that you can return to it easily in the future.

3. In the Username field, enter your username as provided by your administrator.

4. In the Password field, enter your user password. You must enter your password using the same case (upper, lower, or mixed) that was used when the password was defined.

5. Click **Log In** or press the Enter key. You may be required to set a new password and then log in again.

6. Click the Select tab to select an application and study. (If you have logged in previously, the last application and study that you selected may already be selected by default.) Click the row of the application you want to use, and click **Select Application**. The Select Study/Pool page appears.

7. Click the radio button for the study or study pool you want to use, then click **Select Study/Pool**. Information about the selected study or pool appears on the Study Data Domains page.

8. Click **Preferences** in the upper right corner of the page. A window with a list of options opens.

9. For the user preference "Start in this tab", select the Safety Review option then click **Save**. When you next log in, the Safety Review tab will appear automatically.

   If you will be using the same study frequently, you can also set the user preference to "Start up with application and study from previous session". (If you are a new user this check box is already checked by default.)

10. Locate the **Help** link at the top right of the page. A **Help** link appears on every Empirica Study page and window to provide detailed information about features and step-by-step information for completing tasks.

11. Make sure that you have set up software as needed to run Empirica Study. A topic describing Prerequisites and Usage Notes is available in the Empirica Study online help. Although you can log in and perform most actions before setting up software according to these prerequisites, you may not be able to perform certain actions described in this guide.

Note: When you are ready to exit Empirica Study, click the **Exit** link in the upper right hand corner of a page. Do not attempt to exit Empirica Study by closing your browser window, because your Empirica Study session may continue to run and use system resources unnecessarily.

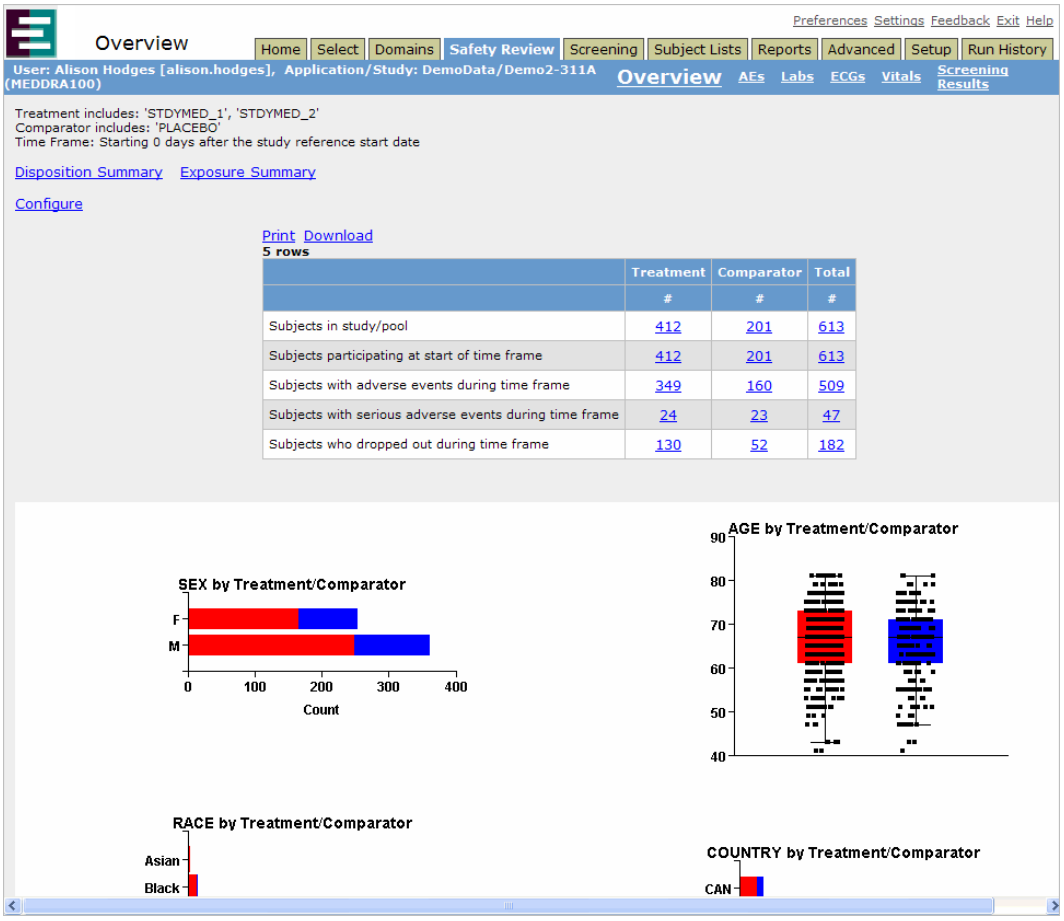
2 Reviewing the Study Population

2.1 Study Population Overview

Before starting your safety review, you can get a general sense of the characteristics of a study population by viewing statistics on the Safety Review Overview page.

To view a study population overview:

1. If you haven't already done so, click the Safety Review tab. The Overview page appears by default. (To return to this page from other Safety Review pages, you can click **Overview** in the blue bar under the Empirica Study tabs.)



2. At the top of the Overview page, information about the study's Treatment and Comparator categories appears followed by information describing the currently selected study time frame. These definitions are created when the study is set up to allow different comparisons and evaluations to be made.

   You can select a different "dosing category breakdown" or time frame for review by clicking **Configure**. All of the configuration options are described in Section 2.3.

3. The Overview page presents a table of subject counts for the study, followed by four graphs showing demographic breakdowns for the study. The table shows the number of subjects in the Treatment category (subjects receiving the treatment drug or drugs), the Comparator category (subjects receiving the comparator drug or drugs), and the Total number of subjects in the study for each of the following:

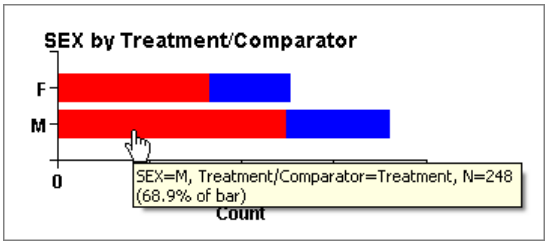
   - Total count of subjects
   - Count of subjects participating at the beginning of the selected time frame
   - Count of subjects who experienced any adverse events in the time frame
   - Count of subjects who experienced serious adverse events in the time frame
   - Count of subjects who dropped out of the study during the time frame

   The four graphs provide a visual display to compare subjects in the Treatment and Comparator categories on the basis of:

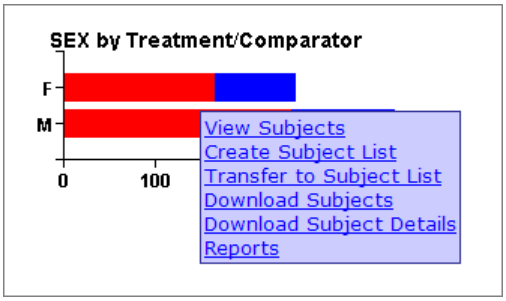
   - Sex
   - Race
   - Age
   - Country

   The bars in the graphs represent the subject counts. A color key appears below the graphs.

4. To review a specific subject count for a bar or area in a graph, hover the mouse cursor over that part of the graph. A "hover help" message appears with an informational summary.

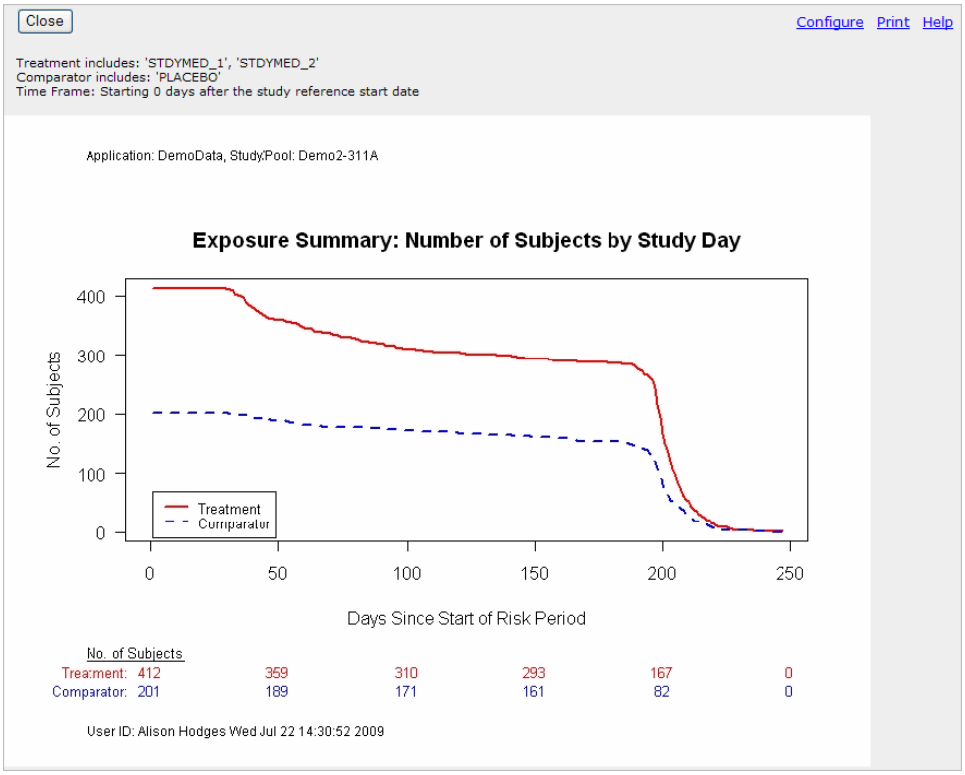


5. You can click an underlined count of subjects in the table or any graph bar to display a "drilldown menu". The drilldown menu, described in more detail in Section 7.1, allows you to explore data by viewing a summary of, and optionally details about, the subjects who comprise a count.



The drilldown feature is available from tables and graphs throughout Empirica Study.

6. To evaluate differences in exposure between the Treatment and Comparator categories over time, click the **Exposure Summary** link at the top left of the Overview page. The Exposure Summary graph opens in a separate window.



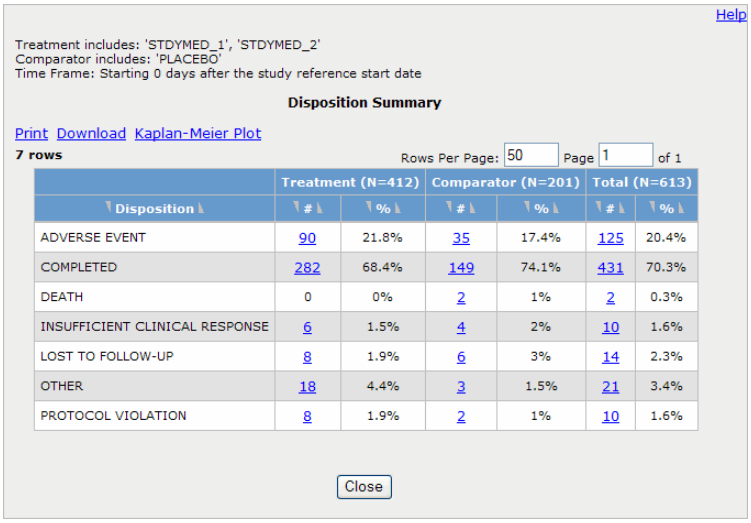
The Exposure Summary shows the number of subjects exposed to the study's treatment or comparator drugs over time. The x-axis represents the number of days since the start of the time period. The y-axis represents the number of subjects exposed. The "No. of Subjects" below the graph shows the count of subjects remaining in the study on each of the study days indicated on the x-axis.

2.2 Occurrences of Death

To identify and explore the occurrence of deaths in the safety population, you can use the Disposition Summary. You can also use the Disposition Summary to review and evaluate other causes of early withdrawal from the study.

To view the Disposition Summary:

1. On the Overview page, click **Disposition Summary**. The Disposition Summary table opens in a separate window showing counts of study subjects who reported each reason for leaving the study. If Death is one of the dispositions in the study data, it appears as a row in the table.



Help

Treatment includes: 'STDYMED_1', 'STDYMED_2'
Comparator includes: 'PLACEBO'
Time Frame: Starting 0 days after the study reference start date

Disposition Summary

Print Download Kaplan-Meier Plot

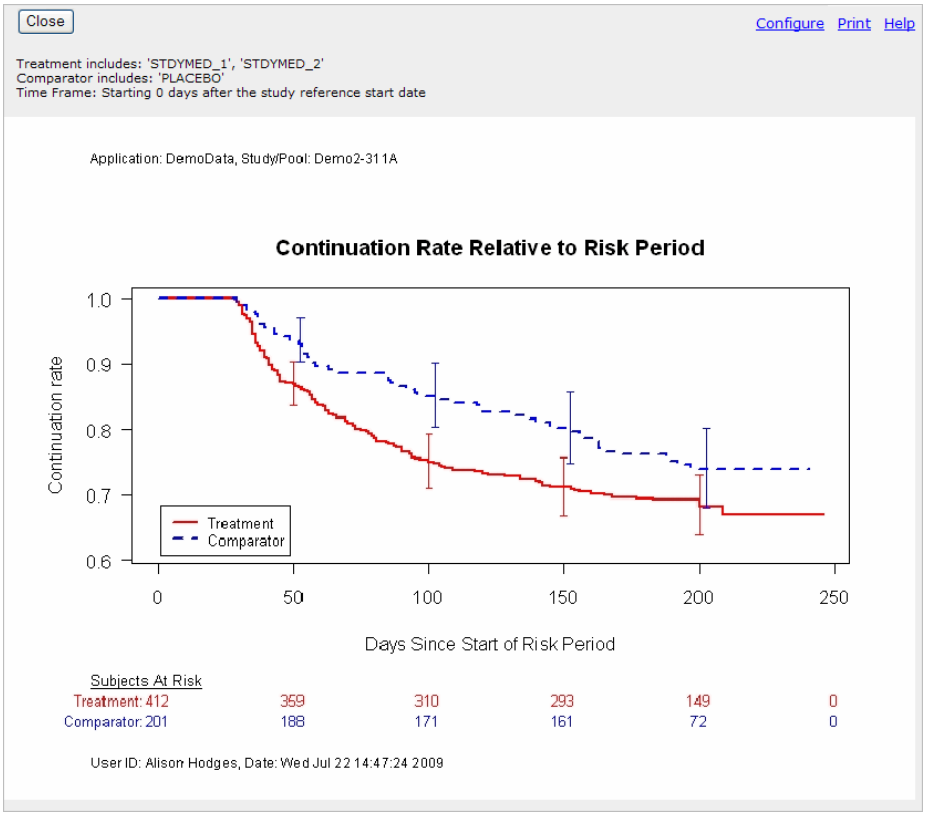
7 rows Rows Per Page: 50 Page 1 of 1

	Treatment (N=412)		Comparator (N=201)		Total (N=613)	
Disposition	#	%	#	%	#	%
ADVERSE EVENT	90	21.8%	35	17.4%	125	20.4%
COMPLETED	282	68.4%	149	74.1%	431	70.3%
DEATH	0	0%	2	1%	2	0.3%
INSUFFICIENT CLINICAL RESPONSE	6	1.5%	4	2%	10	1.6%
LOST TO FOLLOW-UP	8	1.9%	6	3%	14	2.3%
OTHER	18	4.4%	3	1.5%	21	3.4%
PROTOCOL VIOLATION	8	1.9%	2	1%	10	1.6%

Close

2. You can click any underlined subject count in the table to display the drilldown menu and view additional detail about the subjects who comprise that count.

3. To display a graphical representation of the subject continuation rate for the time period under review click **Kaplan-Meier Plot**. The graph opens in a separate window.



The x-axis represents the number of days since the start of the time period. The y-axis represents the proportion of subjects remaining in the study, adjusted for censoring (that is, adjusted for subjects who have completed the study). A 95% confidence interval appears for each study day identified on the x-axis. (To prevent overlapping of the confidence interval depictions for the Treatment and Comparator categories, the confidence interval depictions are slightly offset from each other.)

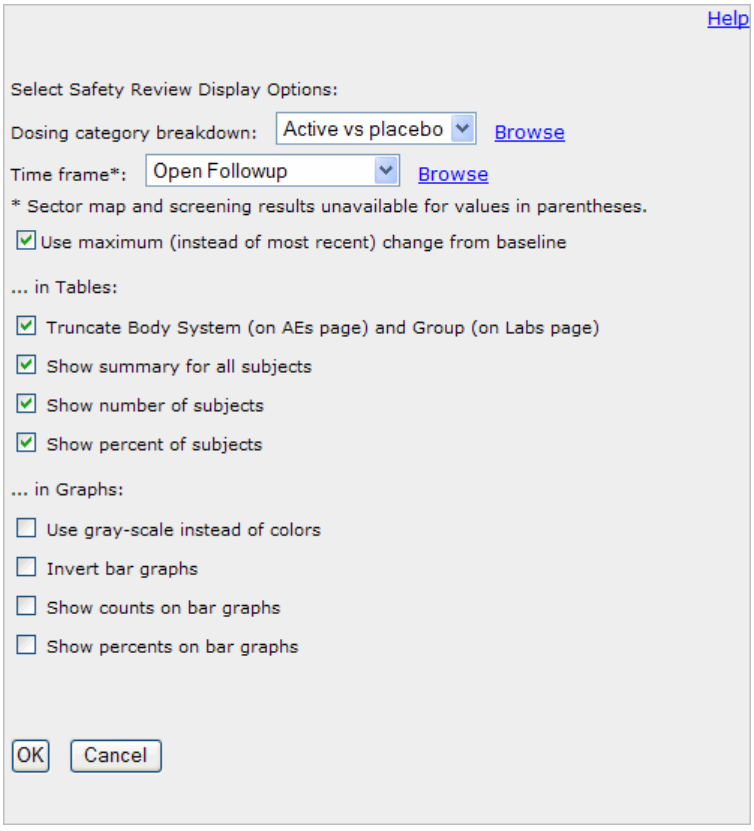
The "Subjects at Risk" section below the graph shows the count of subjects remaining in the study at each day identified on the x-axis.

2.3 Safety Review Configuration

On the Safety Review tab's Overview page the **Configure** link provides access to settings that affect the way data appears throughout the pages accessible from the Safety Review tab. The default settings for these options are expected to be appropriate in most situations, but there may be times when you want to change these settings as described below. This guide assumes that the default settings are in effect.

To set safety review configuration options:

1. On the Safety Review tab click **Overview**.
2. Click **Configure**. The current settings for the configuration options appear in a separate window.



3. Review the configuration options. When changed, these options affect all pages within the Safety Review tab.

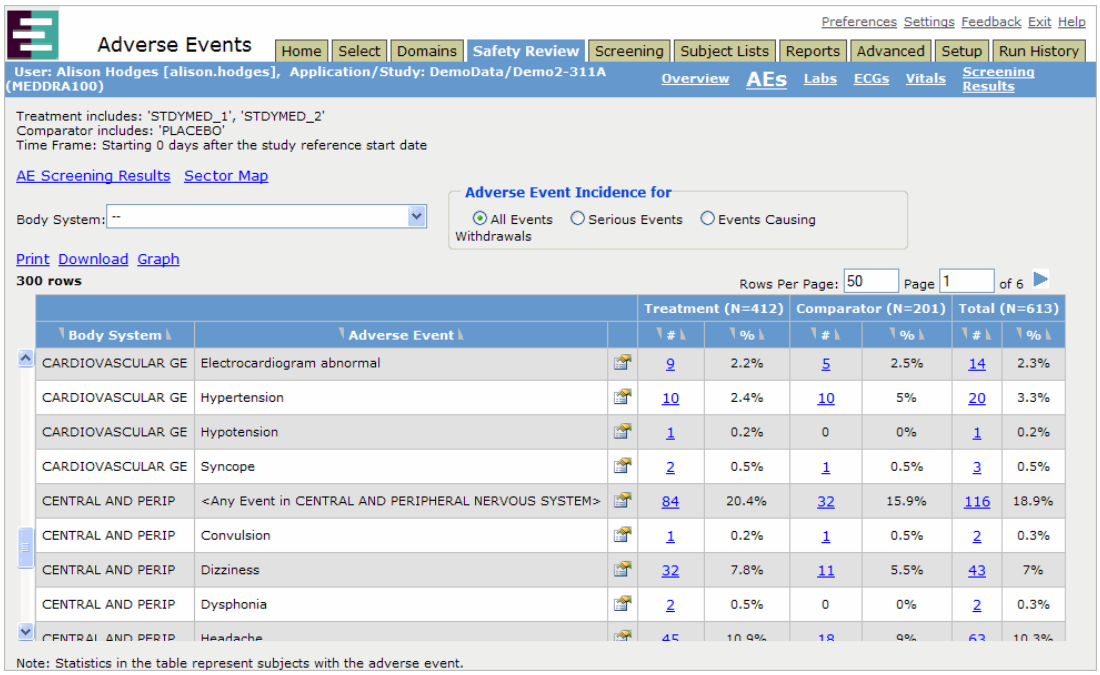
Display Option	Description	Default
Dosing category breakdown	Allows you to select one of the dosing category breakdowns (if any) defined for the study or study pool, or select None to use the ARM values in study data. In order for you to access all of the features available from the Safety Review tab, a screening analysis must exist for the dosing category breakdown that you select.	The study's default dosing category breakdown
Time frame	Allows you to select one of the time frames (if any) defined for the study or study pool or None. Time frames are a property of a study or study pool. A time frame indicates which parameters to use as start date and end date boundaries. For example, a single study could have a time frame for screening through run-in, another for treatment with the experimental drugs, and another for follow-up. In order for you to access all of the features available from the Safety Review tab, a screening analysis must exist for the study time frame that you select.	The study's default time frame
Use maximum (instead of most recent) change from baseline	If checked, the change from baseline values shown on the Vital Signs page and in certain displays from the Lab Results page are computed using the post-baseline result (within the time frame) that has the value with the greatest (positive or negative) change from the baseline result. Otherwise, the change from baseline is computed using the most recent non-null post-baseline result within the time frame.	Same as the selection for the basic screening analysis
Truncate Body System (on AEs page) and Group (on Labs page)	If checked, the Adverse Events page displays a truncated version of the body system name and the Lab Results page displays a truncated version of the panel or group of tests.	Checked
Show summary for all subjects	If checked, tables of statistics include a Total column showing the total count of subjects in the dosing categories.	Checked
Show number of subjects	If checked, tables of statistics include a column showing the count of subjects for each row.	Checked
Show percent of subjects	If checked, tables of statistics include a column showing the percentage of subjects for each row.	Checked
Use gray-scale instead of colors	If checked, graphs use shades of gray instead of colors. Graphs that have a separate gray-scale configuration option are not affected.	Unchecked
Invert bar graphs	If checked, the orientation of the bar graphs on the Overview page is changed to invert the x-axis and y-axis.	Unchecked
Show counts on bar graphs	If checked, the bar graphs on the Overview page show a count of subjects represented by each bar.	Unchecked
Show percents on bar graphs	If checked, the bar graphs on the Overview page show the percentage of subjects represented by each bar.	Unchecked

4. Click **OK** or **Cancel** to close the configuration settings window.

3 Reviewing Adverse Events

To review adverse events:

1. On the Safety Review tab, click **AEs**. The Adverse Events page appears.



   The table on this page presents adverse event incidence information for the selected dosing categories and time frame. The table includes a row for each adverse event, a row for <Any Body System> and <Any Event>, and a row for <Any Event> in each body system. Subject counts and percentages for subjects reporting an event from each of the Treatment, Comparator, and Total (all subjects in Treatment and Comparator) categories are shown. The N after each column heading shows the total count of subjects for that group.

2. You can click radio buttons in the "Adverse Event Incidence for" area above the table to restrict the listed events to those that are serious or to those that resulted in withdrawal from the study.

   Note: The radio buttons only limit the data that appears on this page. They do not affect the data that appears if you choose to view AE Screening Results or a Sector Map.

3. To view only events for a particular body system, select a value in the Body System field. ("--" indicates all body systems.)

   Note: This selection affects only the current page and does not affect the data on the AE Screening Results page or a Sector Map.

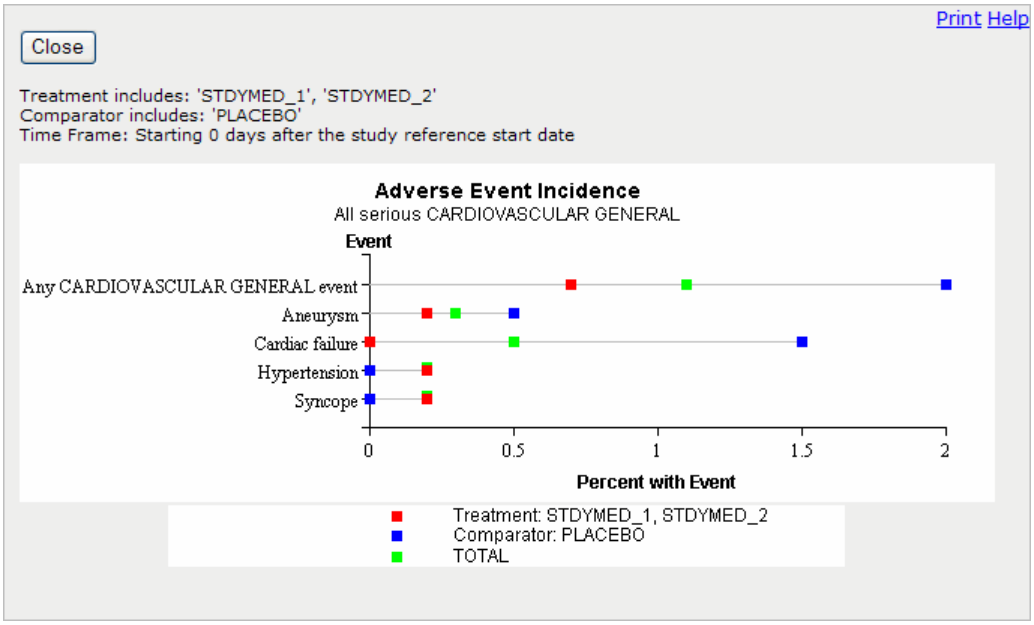
4. A table may include multiple "pages". To control how many rows display on each page, enter a number in the Rows Per Page field and press the Enter key.

5. To go to a different page of the table, you:
   - Click ▶ to a view the next page.
   - Click ◀ to view the previous page.
   - Enter a number in the Page field and press the Enter key to view a specific page.

6. To sort the table by the data in a particular column, click either the down arrow (for descending order) or the up arrow (for ascending order) on either side of a column heading.

   For example, to determine frequently occurring adverse events, sort the table in descending order by the # or % column for the Treatment, Comparator, or Total group.

7. To view a graph of adverse event incidence, click **Graph**. A dot plot of the adverse events currently shown in the table opens in a separate window.



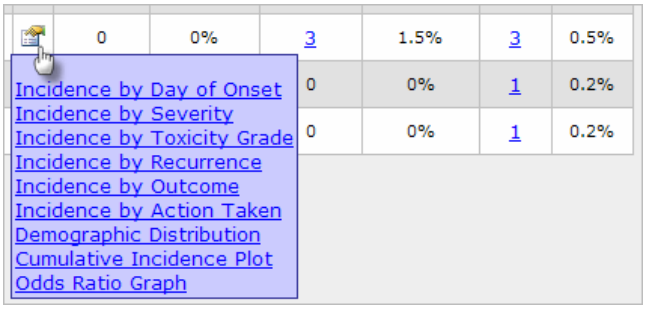
This graph, as well as the other AE incidence graphs described below, uses the following key:

Treatment	Percentage of Treatment category subjects who experienced the adverse event
Comparator	Percentage of Comparator category subjects who experienced the adverse event
TOTAL	Percentage of subjects in the Treatment and Comparator categories who experienced the adverse event

3.1 Exploring Adverse Event Incidence

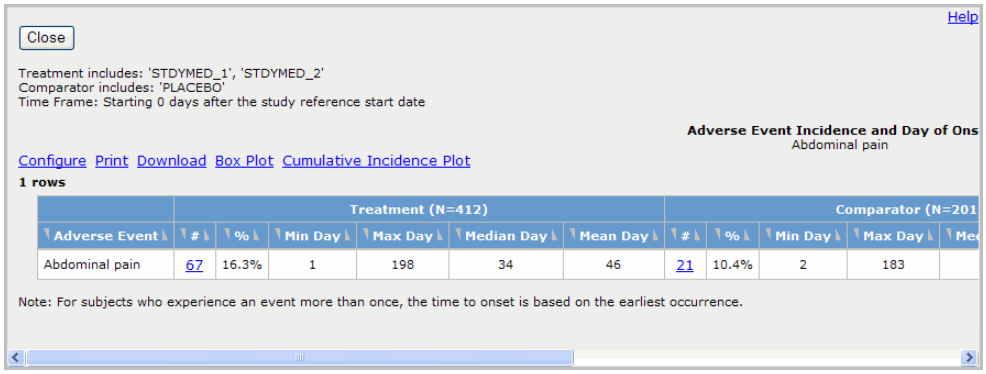
To view adverse event incidence by various factors:

1. On the Adverse Events page, click  next to an event to display the following menu:

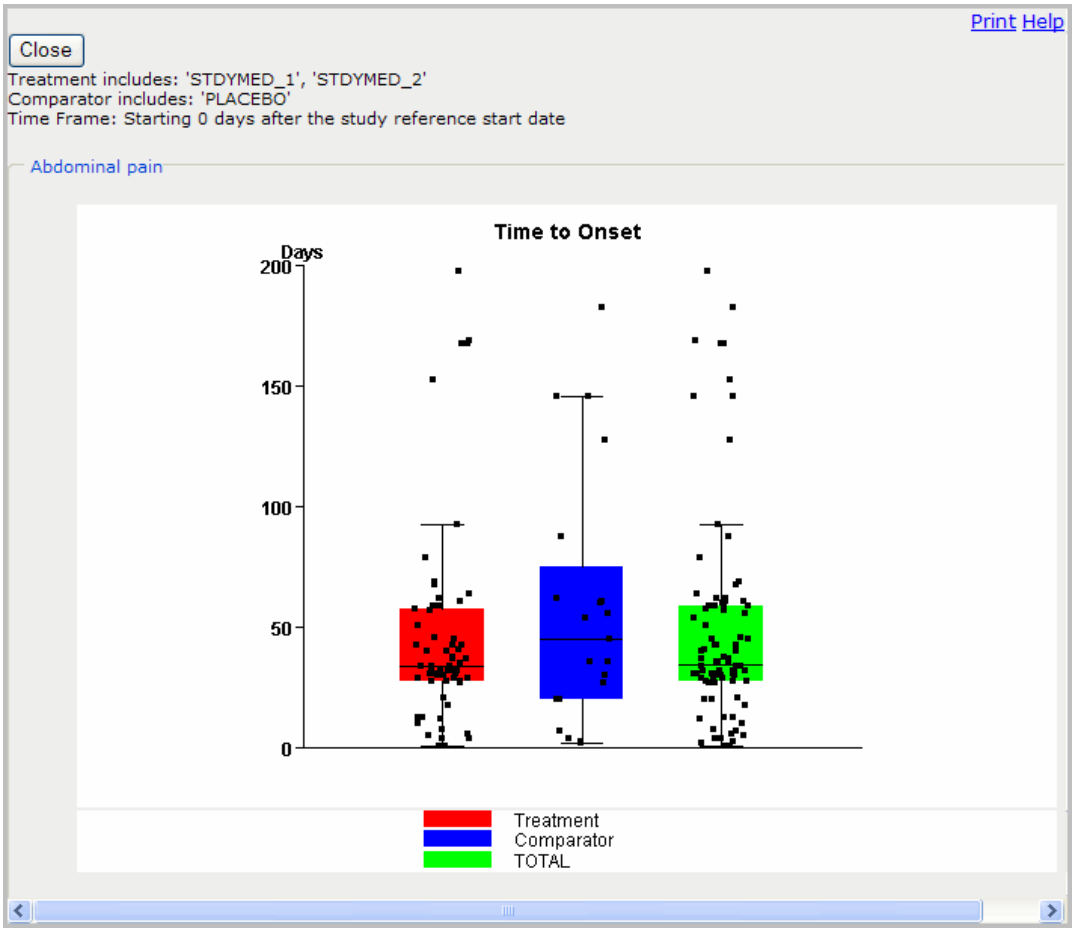


Each of these options provides more detailed information about the incidence of that adverse event.

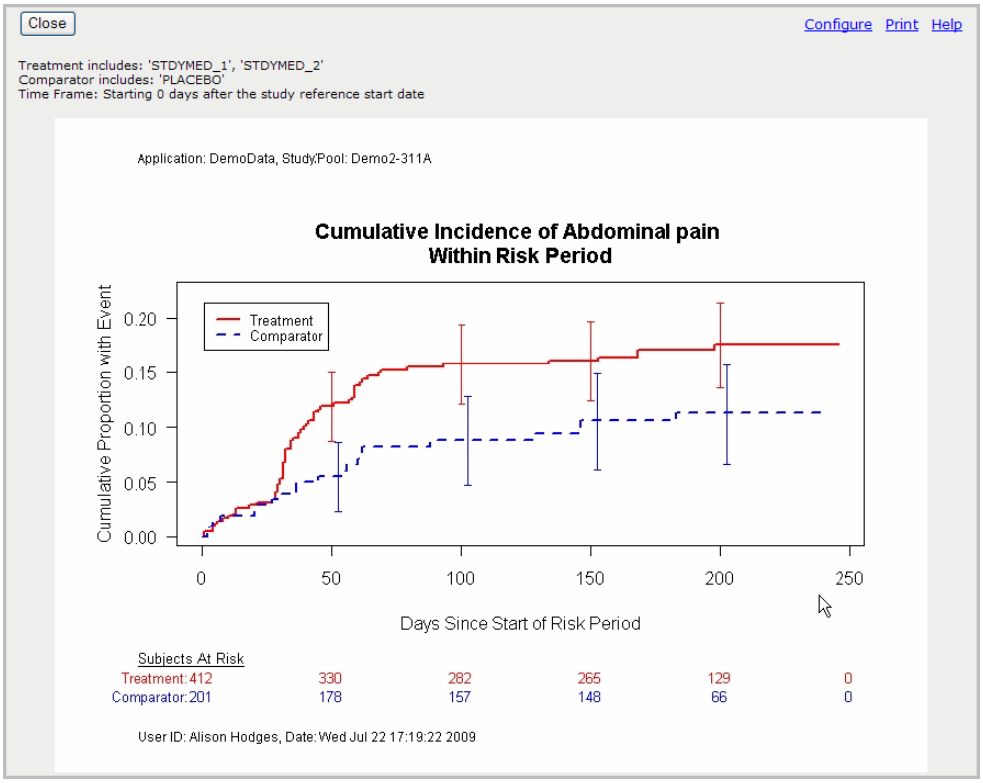
2. Select the **Incidence by Day of Onset** option to show the count, percentage, minimum, maximum, median, and mean day of onset for subjects reporting the adverse event.



3. Two options are available to display Day of Onset data graphically. To display a graph of the distribution of time to onset for each dosing category and the total, click **Box Plot** in the Incidence by Day of Onset window.

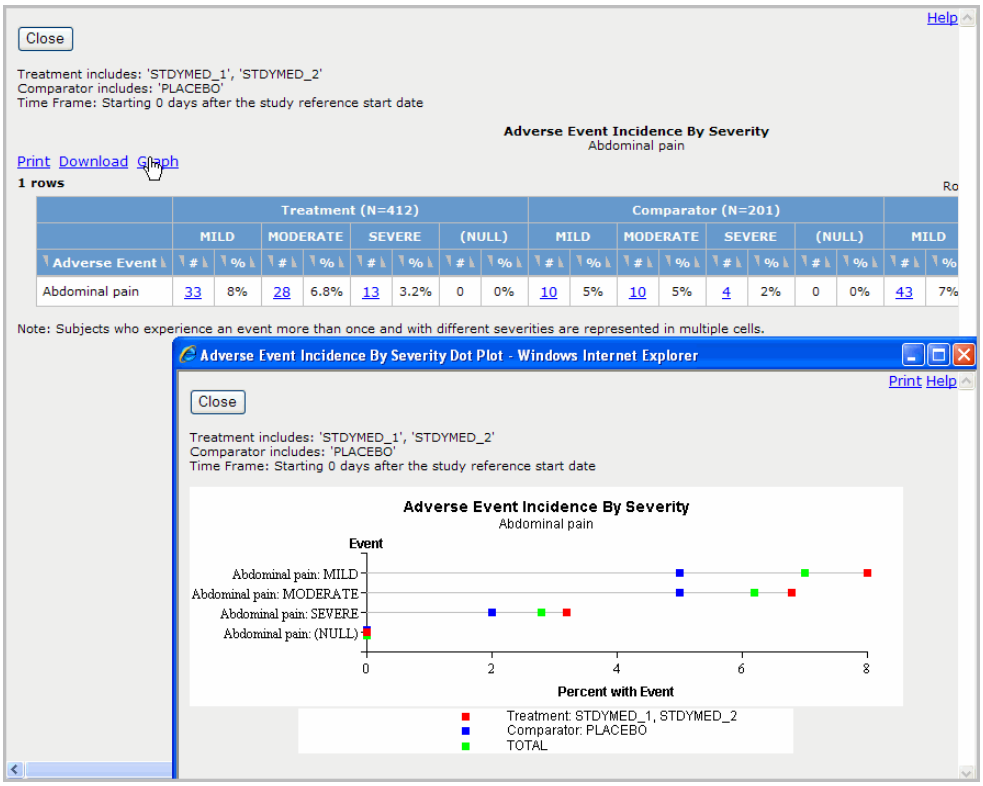


To display a graphical representation of the cumulative incidence of the event, click **Cumulative Incidence Plot** in the Incidence by Day of Onset window.



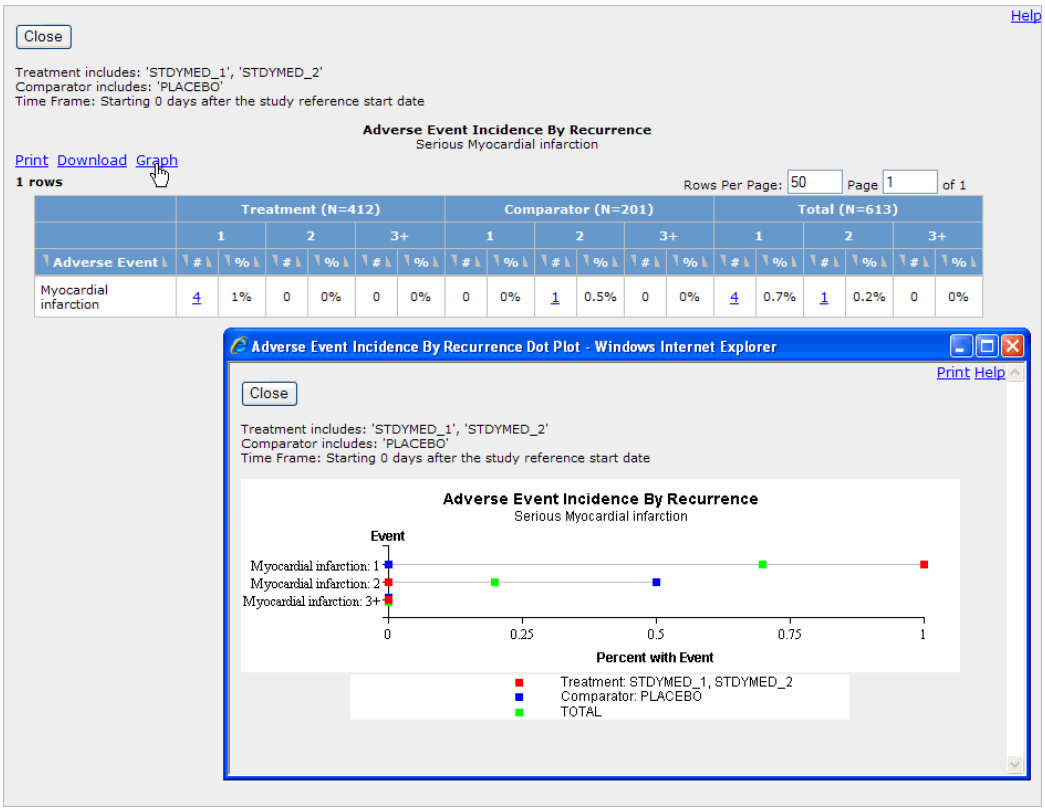
4. Select the **Incidence by Severity**, **Toxicity Grade**, **Outcome**, or **Action Taken** options to show the count and percentage of subjects reporting the adverse event with each qualifier. For example, the Incidence by Severity table shows counts for Mild, Moderate, and Severe occurrences of the event.

   To display the information in any of these incidence tables graphically click **Graph**.

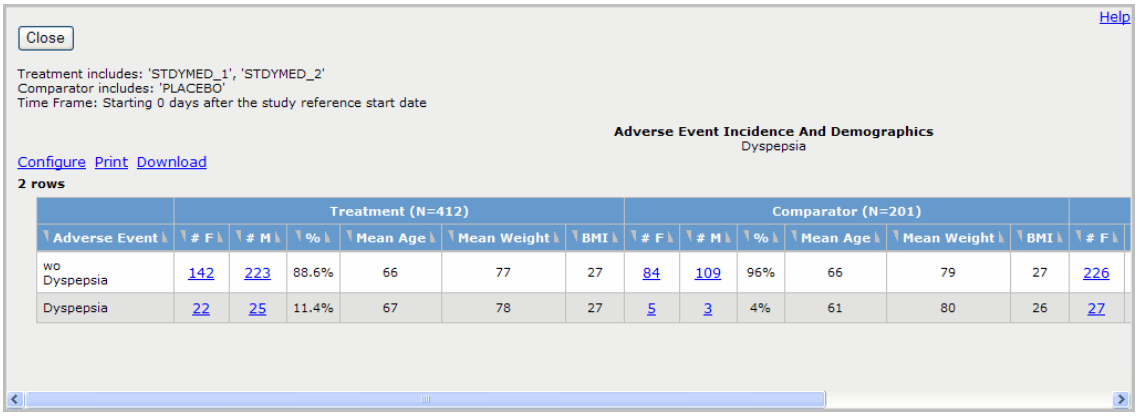


5. Select the **Incidence by Recurrence** option to show the count and percentage of subjects who have reported one or more occurrences of an adverse event. The 1 column represents subjects with one occurrence of the event; the 2 column represents subjects with two occurrences of the event; and the 3+ column represents subjects with three or more occurrences of the event.

   To display the information in this table graphically click **Graph**.



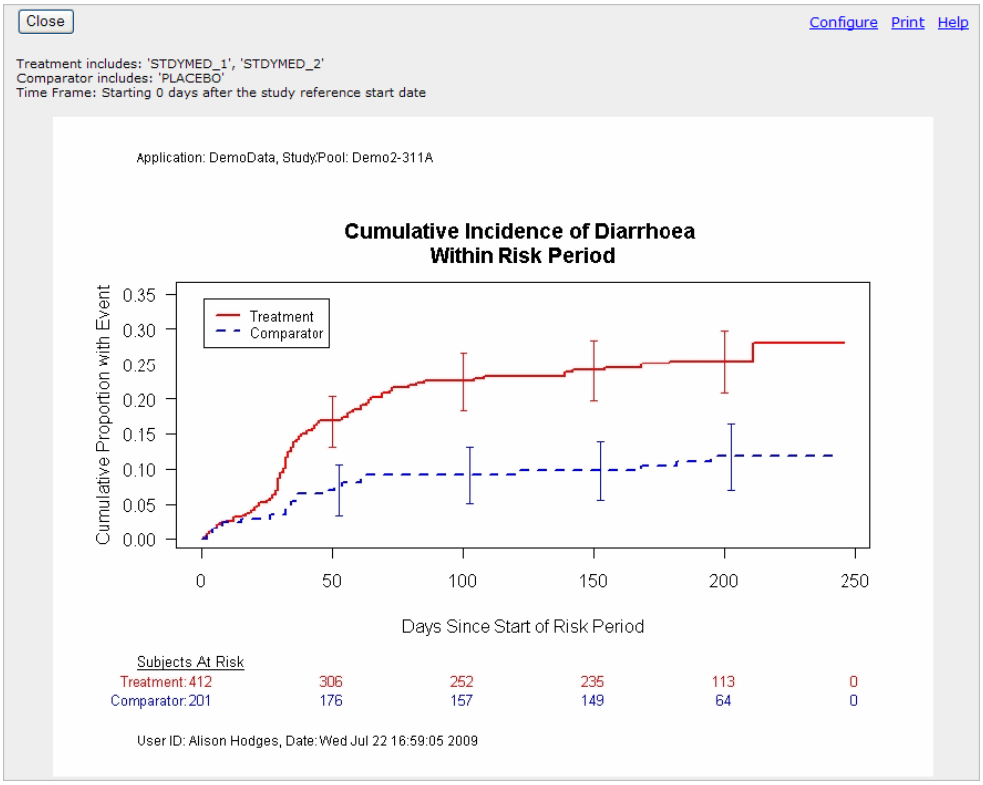
6. Select the **Demographic Distribution** option to show the count, percentage, mean age, mean weight, and mean Body Mass Index for subjects without (wo) and with the adverse event.



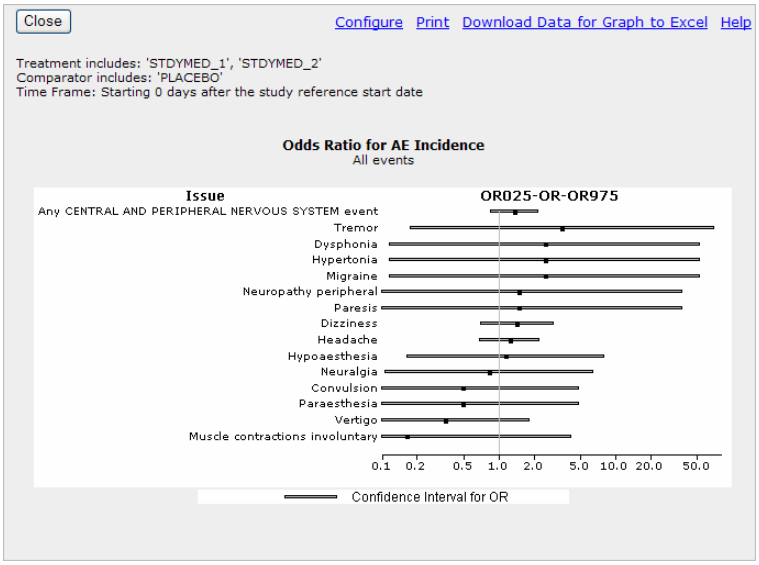
7. Select the **Cumulative Incidence Plot** option to show an adverse event's time to onset across Treatment and Comparator categories. Curves in the graph are for Kaplan-Meier estimates. Each curve ends when all subjects have either experienced the adverse event or completed or left the study. The x-axis represents the study day, and the y-axis represents the cumulative proportion of subjects with the adverse event, adjusted for censoring. A 95% confidence interval appears at each study day. To

prevent overlapping of the confidence interval depictions for Treatment and Comparator categories, the confidence interval depictions are slightly offset from each other.

The "Subjects at Risk" section below the graph shows the count of subjects remaining in the study who have not experienced the adverse event at each study day identified on the x-axis.



8. Select the **Odds Ratio Graph** option to show the corrected odds ratio calculated for the adverse event with lower and upper confidence bounds. In the following example, this option was selected for one of the <Any Event in body system> rows in the Adverse Events table: the graph plots the corrected odds ratio for that event category and for each of its component events.



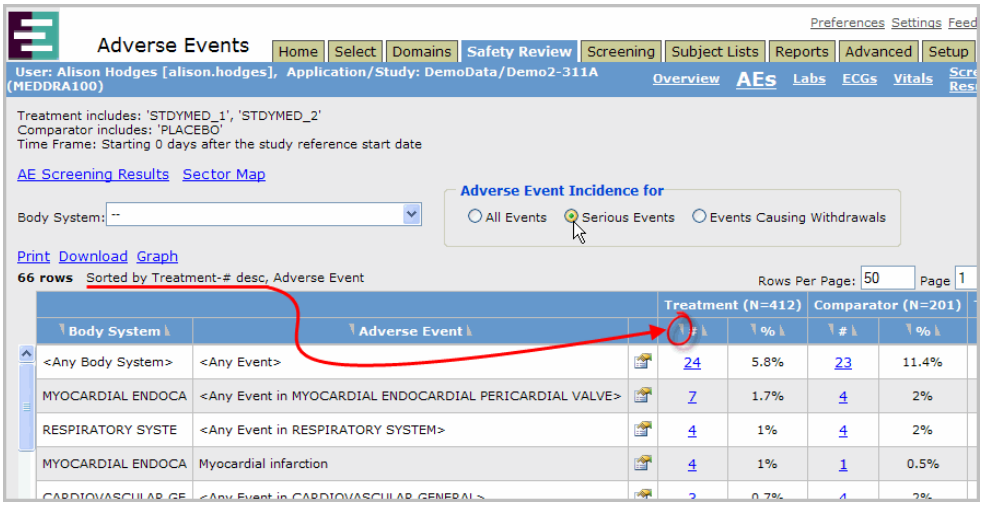
3.2 Serious Adverse Events

To review serious adverse events:

1. On the Adverse Events page, click the **Serious Events** radio button. The table updates to include rows for serious adverse events only.

2. To list frequently occurring serious adverse events, you can sort the total count in descending order by using the down arrow on the left side of the # column heading under “Total”.

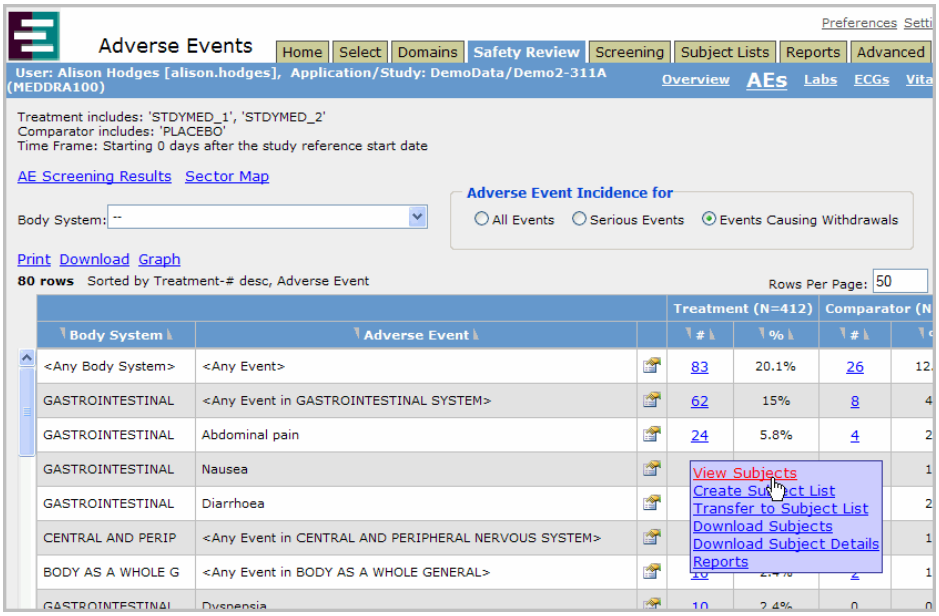
   To list events occurring more frequently in the Treatment or Comparator group, you can sort in descending order of the # column under “Treatment” or “Comparator”.



3.3 Study Dropouts

To review events leading to study dropouts (study withdrawal):

1. On the Adverse Events page, click the **Events Causing Withdrawals** radio button. The table updates to include rows for only those adverse events leading to study dropout.
2. To investigate reasons for study withdrawal for subjects with a particular adverse event, drill down on a subject count, select **View Subjects**, then view the **Napoleon's March** graph as described in Section 7.1.



3.4 Relationship of Adverse Events to Study Drug

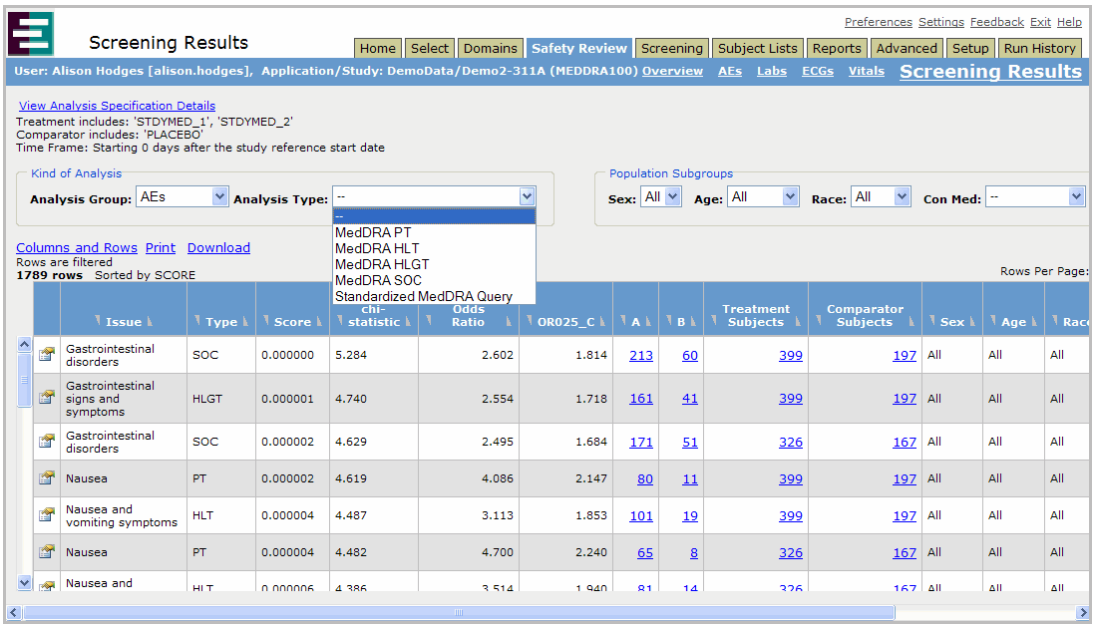
Screening analysis is the process of computing statistical scores for associations between a treatment group (rather than a comparator or total group) and an issue. The "issue" can be one of several different types of safety issues. For example, in a MedDRA PT disproportionality analysis, the issue is a particular adverse event PT (preferred term). In a clinically significant lab analysis, each lab result is an issue.

Screening analysis results are generated when a screening analysis specification is created and run by a user with appropriate Empirica Study permission settings. A screening analysis specification defines subgroups of subjects (based on factors such as sex, race, age, medical history, and concomitant medications) and includes one or more analysis types, such as the MedDRA PT disproportionality analysis and clinically significant lab analysis mentioned above. When the screening analysis specification is run, one or more of the study's dosing category breakdowns and time frames are selected and computations are made for each one.

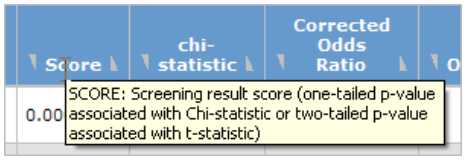
You may not be responsible for creating and running screening analysis specifications. Typically, a basic, comprehensive screening analysis specification is created and run for each study when it is set up. The results of that screening analysis, as well as any others defined later, are available on the Safety Review tab when you choose to view screening results.

To review the relationship of adverse events to the study drug:

1. On the Adverse Events page, click **AE Screening Results**. The Screening Results page appears.
2. In the Analysis Group field, AEs is selected by default since you used the **AE Screening Results** link to navigate to this page. The Analysis Type field shows "--", which includes all analysis types that involve AEs. For example, you can select an analysis type to limit your review to results computed for a single level of the MedDRA hierarchy (based on the primary path of the reported Preferred Term).



3. The Population Subgroups area above the table offers a field for each subject subgroup defined for the analysis specification that generated the screening analysis results. Subjects with a particular category value (such as with an Age of Over 50) comprise a subgroup of subjects. You can limit your review to results for a single subgroup by selecting one of these values.
4. The following table describes some of the columns available in the AE screening results table. To display a description of any columns in this table, use the mouse to hover the cursor over the column heading.



The following table describes some of the columns available in the AE screening results table.

Column	Description
Issue	The safety issue. For a MedDRA PT, HLT, HLGT, or SOC Analysis, a specific MedDRA term. For a Standardized MedDRA Query Analysis, a specific SMQ.
Type	Abbreviation of the type of analysis performed to generate the results. PT, HLT, HLGT, and SOC correspond to the MedDRA PT, MedDRA HLT, MedDRA HLGT, and MedDRA SOC analysis types, and SMQ indicates Standardized MedDRA Query.
Score	The statistical screening result. Lower scores are more "interesting".
chi-statistic	The chi-statistic value.

Column	Description
Corrected Odds Ratio	The corrected odds ratio statistic: [(A + 0.5)(D + 0.5)] / [(B + 0.5)(C + 0.5)].
OR025_C	The lower confidence bound of the corrected odds ratio statistic.
A	The count of subjects who received the study treatment and experienced the issue within the time frame.
B	The count of subjects who received the study comparator and experienced the issue within the time frame.
Treatment Subjects	The total count of subjects who received the study treatment and have sufficient data to determine if the issue occurred.
Comparator Subjects	The total count of subjects who received the study comparator and have sufficient data to determine if the issue occurred.

You can click **Columns and Rows** to select columns to display, define the order in which they appear, and specify a sort order. You also have the option to specify a SQL Where clause to filter rows.

5. You can also sort table data by clicking the up or down arrow on either side of a column heading.

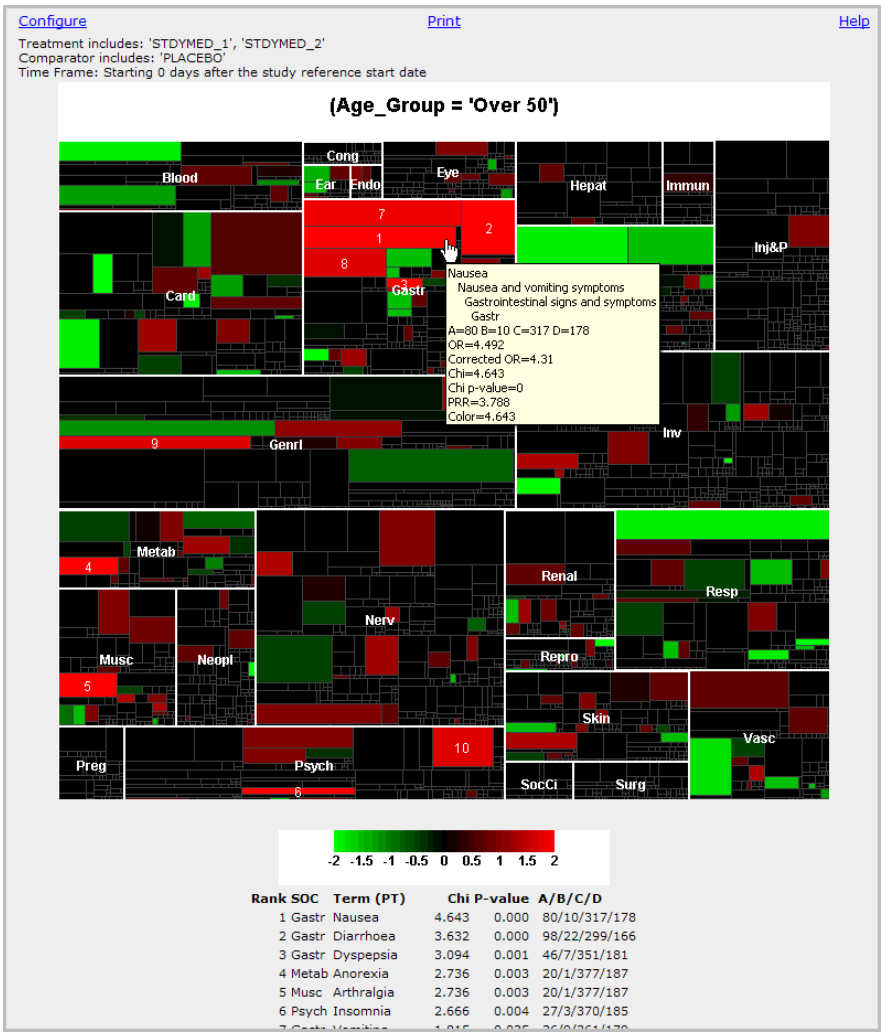
   The more interesting results have lower values of Score, where “interesting” is when subjects in the treatment group experience a disproportionately higher occurrence rate of an adverse event than do subjects in the comparator group. To show more interesting results first in the table of results, sort the table in ascending order of Score.

To view a sector map:

A sector map is a visual presentation of adverse event terms that appear in the study data and are reported using MedDRA terms. The sector map presents each SOC as a large rectangle or tile, and presents PTs (or another hierarchy level) in that SOC as smaller tiles with different colors and sizes. The primary path of a term determines where it appears in the sector map. The visual comparison of the colors and sizes of the tiles can provide a "big picture" overview of the adverse event profile of a drug.

1. On the Screening Results page (on the Safety Review tab), select the analysis type MedDRA PT.

2. Click **View Sector Map**. The graph appears in a separate window.



A ranking of the terms with the highest chi-statistic values appears below the sector map. The rank number also appears on the tiles for those terms.

3. When you use the mouse to point to a tile, the following information appears:
   - The name of the MedDRA PT and its HLT, HLGT, and SOC
   - A/B/C/D – Counts from the 2x2 table for observed subjects used to compute results (see the next section for information on viewing additional information for an issue including the 2x2 table)
   - OR/Corrected OR –Modified odds ratio and Corrected odds ratio
   - Chi – chi-statistic
   - Chi p-value – p-value associated with the chi-statistic.
   - PRR – Proportional Reporting Ratio
   - Color – Numeric indication of the relative intensity of the color, according to the color key below the sector map.

4. When you click on a tile of the graph and there are one or more subjects with the treatment or comparator drug and the term represented by the tile, a menu appears and you can do the following:

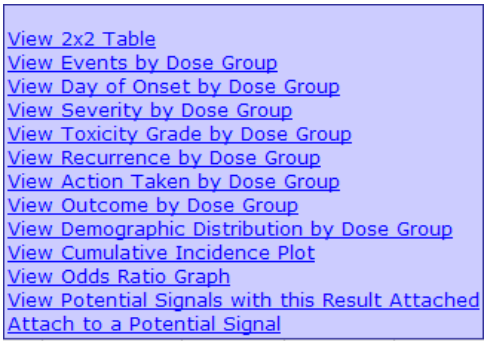
- Click **2x2 Table** to view 2x2 tables (for observed subjects and expected subjects).
- View a **Cumulative Incidence Plot**.
- Drill down to subjects with a combination of the treatment drug and the term represented by the tile.

You can also click **Zoom** to display data for the SOC only.

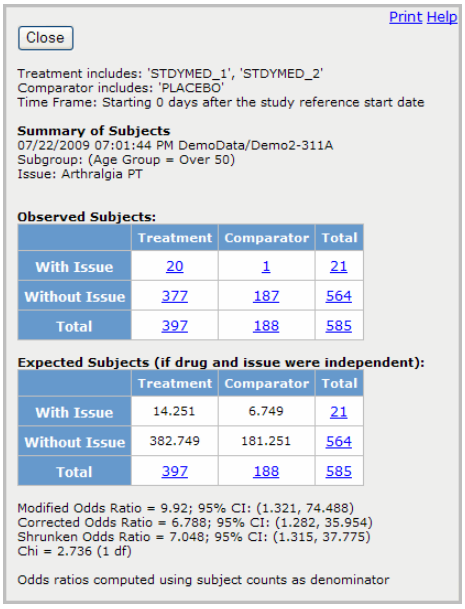
5. To configure the sector map, click **Configure**. Click **Help** for information about the available configuration options.

To view additional information for an issue:

1. On the Screening Results page, if you click  for an issue the following menu of options appears:



2. When you click **View 2x2 Table** the contingency table used to generate screening results appears in a separate window. The 2x2 table of observed subject counts, and the 2x2 table of expected subject counts, display.

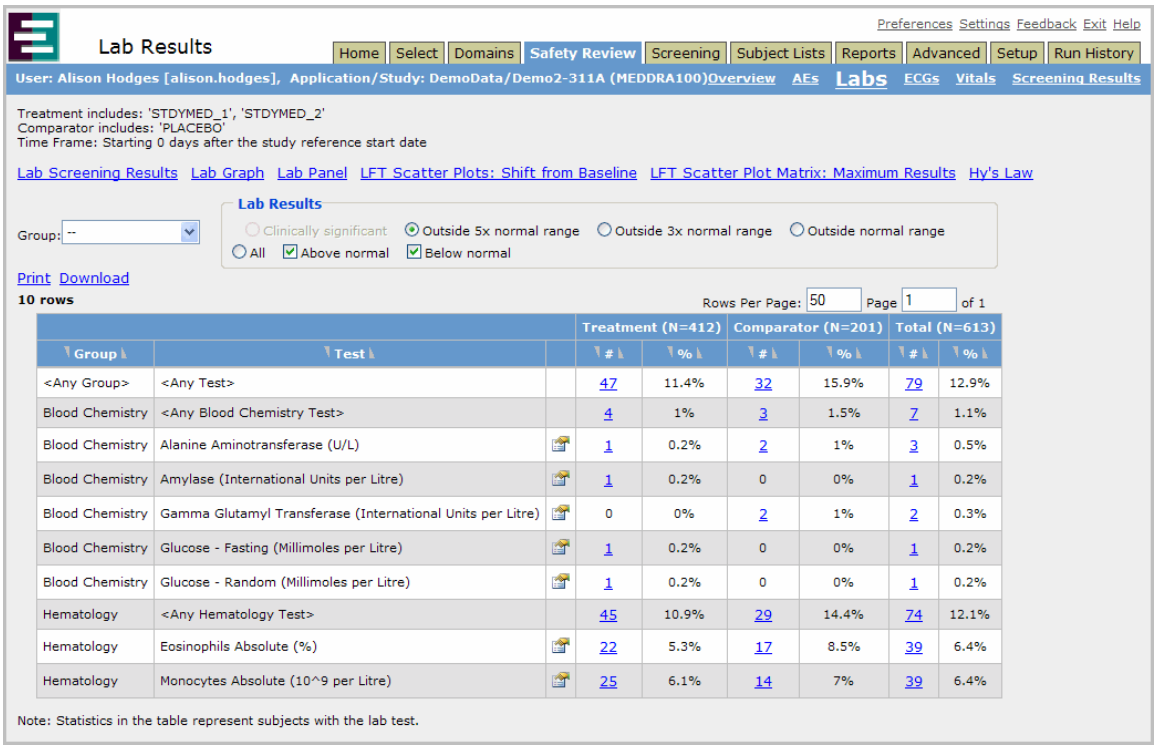


3. Other options on the menu are similar to the options that are available for one of the rows on the Adverse Events page. For information about all of the options, click **Help**.

4 Reviewing Lab Results

To review lab results:

1. On the Safety Review tab, click **Labs**. The Lab Results page appears.



   The table includes a row for each lab test, a row for <Any Group> and <Any Test>, and a row for <Any Test> in each group. Subject counts and percentages for lab tests in the study are shown.

2. Optionally select a panel of tests, such as Blood Chemistry, in the Group field. The table updates to show only rows for tests in the selected panel.

3. By using the radio buttons in the "Lab Results" area above the table, you can limit the results in the table to those that fall into specified ranges in relation to normal. Click one of the following radio buttons to restrict which results are listed:

Lab Results	Description
Outside 5x Normal Range	A post-baseline value is either of the following: • Less than a fifth of the lower end of the normal range. • Greater than five times the upper end of the normal range.
Outside 3x Normal Range	A post-baseline value is either of the following: • Less than a third of the lower end of the normal range. • Greater than three times the upper end of the normal range.
Outside Normal Range	A post-baseline value is either of the following: • Less than the lower end of the normal range. • Greater than the upper end of the normal range.
All	Any value.

Note: The **Clinically Significant** radio button is only available if a lab test clinical significance flag variable has been defined for the study.

4. You also have the option to use the "Above normal" and "Below normal" checkboxes. These checkboxes work in conjunction with the selected radio button to limit the results displayed in the table to only those that are above normal, only those that are below normal, or results that are either above or below normal.

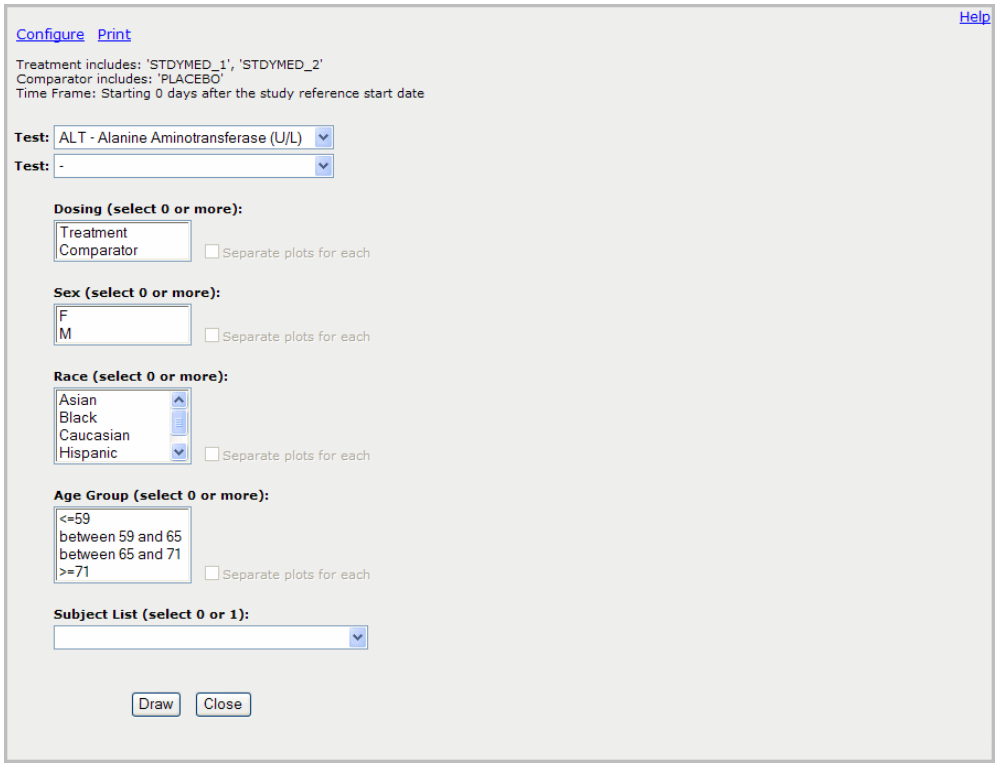
   Note: The options in the Lab Results section and the Group field affect only the current page, not the features that display when you use the options on the line that begins **Lab Screening Results**.

4.1 Lab Results for Subgroups

You can view lab results for subgroups of subjects by displaying a Lab Graph or Lab Panel. A Lab Graph shows lab result values for one or two individual lab tests over the course of the study for a specific set of subjects. A Lab Panel provides a "heat map" visual representation of lab test values that are outside of normal ranges.

To view a lab graph:

1. On the Lab Results page, click **Lab Graph**. The Lab Graph page opens in a separate window with a set of options for displaying the graph on the left side.



2. You can plot up to two lab tests on the same graph: select one or two tests. If you choose two tests, the graph plots values using different shapes to distinguish them. A key appears below the graph.

3. For Dosing, Sex, Race, and Age Group, select values defining the subgroup for which you want to view lab results. To select more than one value in a list, hold down the Ctrl key while you click each one.

   You also have the option to produce "Separate plots for each" of these subgroups. If you check this checkbox, the graph plots the values using different colors to distinguish the values selected. A key appears below the graph.

4. In the Subject List field, optionally select a subject list. The Lab Graph will include only subjects in the selected subject list.

   Note: A "subject list" is simply a saved list of subjects of interest. Existing subject lists are listed on the Subject Lists tab. Subject lists can be produced in a variety of ways. For example, you can create a subject list containing only subjects that meet specified query criteria, or you can create a subject list from drilldown information (described in Section 7.1).

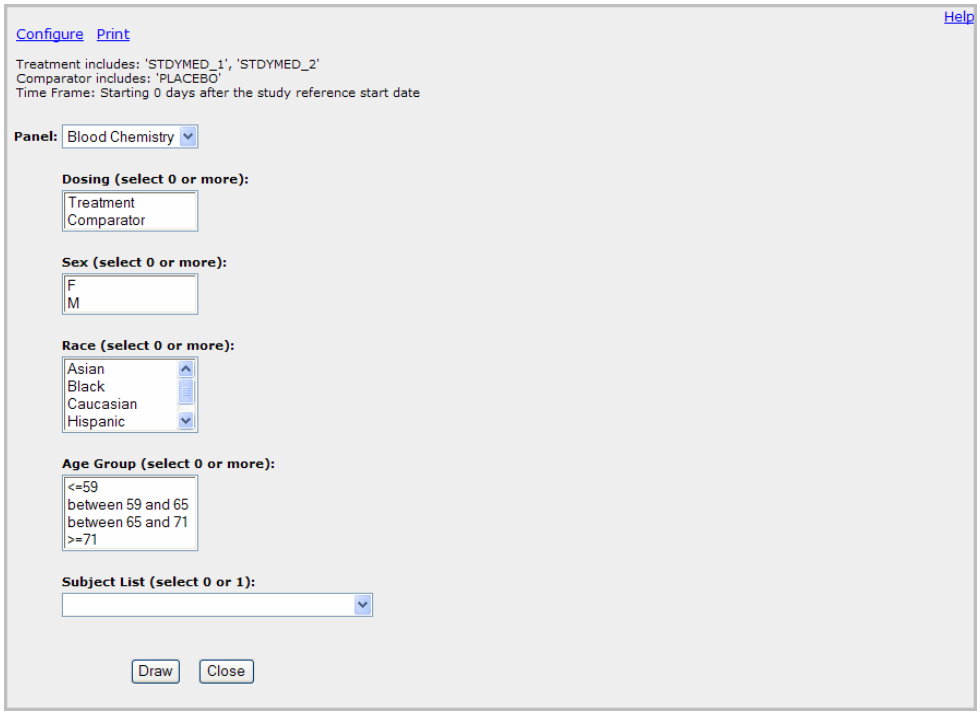
5. Click **Draw**. The lab graph appears in the same window.

   Data points within the gray area of the graph fall within normal ranges of test values. The graph uses different sizes, larger or smaller circles or triangles, to indicate clinically significant values.

6. To configure the graph, click **Configure**. Click **Help** for information about the available configuration options.

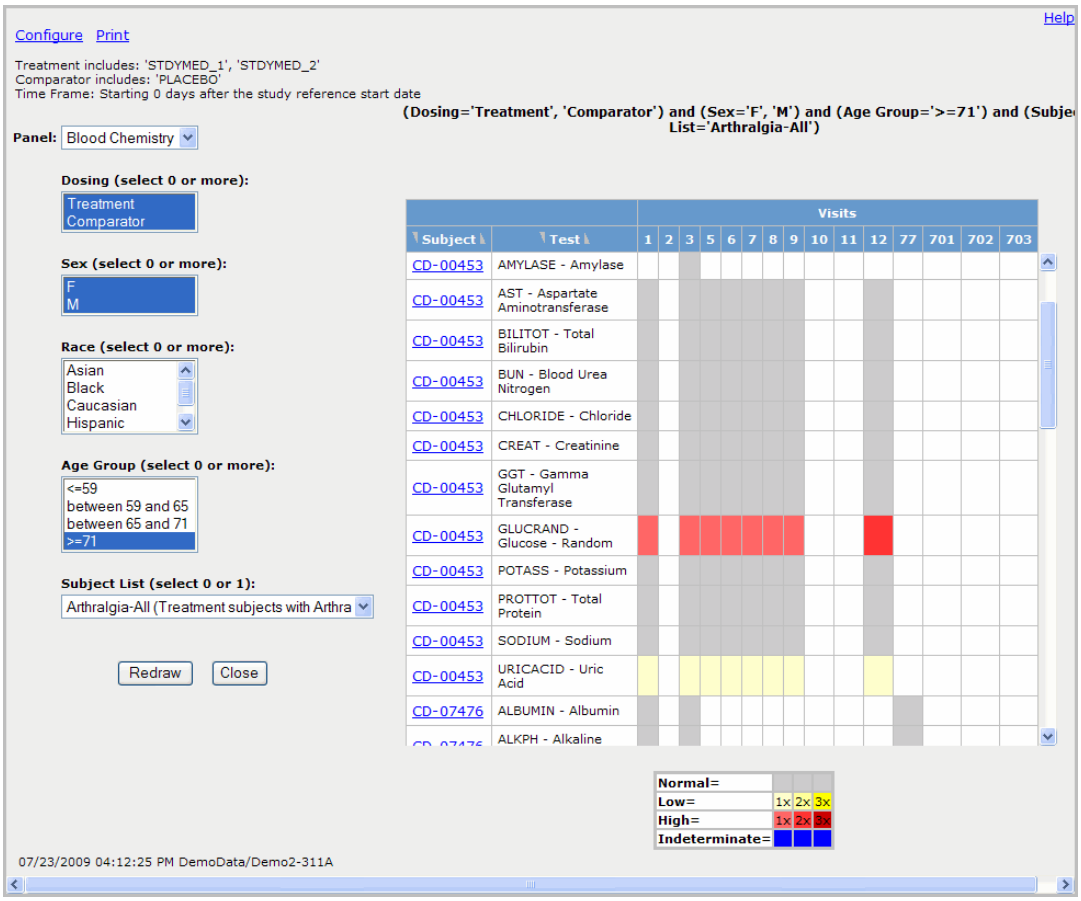
To view a lab panel:

1. On the Lab Results page, click **Lab Panel**. A separate window opens with controls for displaying a lab panel graph.



2. Select a panel of tests in the Panel field.
3. For Dosing, Sex, Race, and Age Group, select values defining the subgroup for which you want to view lab results. To select more than one value in a list, hold down the Ctrl key while you click each one.
4. In the Subject List field, optionally select a subject list. The lab panel graph will include only subjects in the selected subject list.

5. Click **Draw**. The lab panel graph appears in the same window.



Additional information for the color key below the graph follows:

Label	Meaning	Example Values if Normal Range is 20-30
Low = 1x	Less than the lower end of the normal range and greater than or equal to half the lower end of the normal range.	10 through 19.999
Low= 2x	Less than half the lower end of the normal range limit and greater than or equal to a third of the lower end of the normal range.	6.667 through 9.999
Low = 3x	Less than a third of the lower end of the normal range.	0 through 6.666
High = 1x	Greater than the upper end of the normal range and less than or equal to twice the upper end of the normal range.	30.001 through 60
High = 2x	Greater than twice the upper end of the normal range and less than or equal to three times the upper end of the normal range.	60.001 through 90
High = 3x	Greater than three times the upper end of the normal range.	90.001 or above

Label	Meaning	Example Values if Normal Range is 20-30
Indeterminate	Any of the following is true: • There is no upper or lower limit for the normal range. • There is no lower limit of normal and the result is not greater than or equal to the upper limit of normal. • There is no upper limit of normal and the result is not less than or equal to the lower limit of normal.	

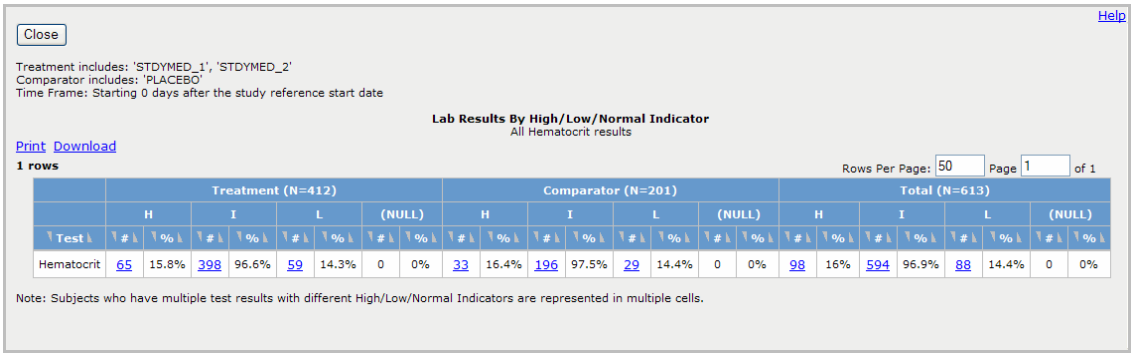
7. When you point to a graph cell, hover help with the following information appears:
   - The lab test value.
   - The lower end of the normal range for the lab test.
   - The upper end of the normal range for the lab test.
8. When you point to a subject ID, hover help with the assigned arm and date of last visit appears.
9. To open a separate window with details for a subject, click the subject ID.
10. To configure the lab panel graph click **Configure**. Click **Help** for information about the available configuration options.

    You can configure the graph to display all data on the same page (as shown above) or with just one test or subject on each page. If you choose to display one test or subject per page, the graph redisplays with a Current Test or Current Subject field that allows you to select a test or subject to view, and **Next** and **Prev** buttons to display the graph for the next or previous test or subject.

4.2 Lab Results by Range Indicators

To view lab results by range indicators:

1. On the Lab Results page, click the All radio button.
2. Click  for a lab test and then click **Results by High/Low/Normal Indicator**. (This option is available only after you select the All radio button.) A separate window opens with the count and percentage of subjects with a lab test result in each range.



Help

Close

Treatment includes: 'STDYMED_1', 'STDYMED_2'
Comparator includes: 'PLACEBO'
Time Frame: Starting 0 days after the study reference start date

Lab Results By High/Low/Normal Indicator
All Hematocrit results

Print Download

1 rows

Rows Per Page: 50 Page 1 of 1

	Treatment (N=412)								Comparator (N=201)								Total (N=613)							
	H		I		L		(NULL)		H		I		L		(NULL)		H		I		L		(NULL)	
Test	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%
Hematocrit	65	15.8%	398	96.6%	59	14.3%	0	0%	33	16.4%	196	97.5%	29	14.4%	0	0%	98	16%	594	96.9%	88	14.4%	0	0%

Note: Subjects who have multiple test results with different High/Low/Normal Indicators are represented in multiple cells.

4.3 Lab Results Distribution over Time

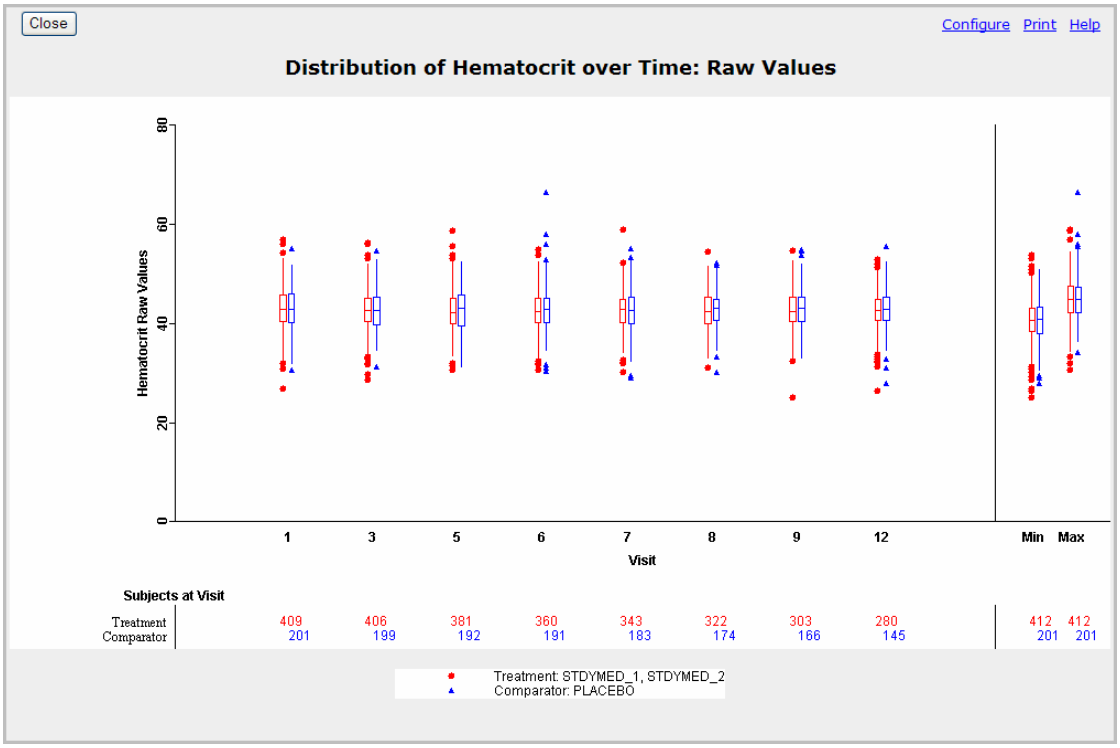
To show the distribution of lab test results over time, you produce a box plot graph that plots normalized lab test values, maximum changes in lab test values, or reported lab test values for subjects in the Treatment and Comparator categories.

To view a box plot showing distribution over time for a lab test:

1. On the Lab Results page, click  for a lab test and click **Box Plot: Distribution Over Time**. This option has three suboptions:

   - **Normalized Raw Values**: actual results from the study data divided by the upper limit of normal
   - **Change from Baseline**
   - **Raw Values**: actual results from the study data

   Select any of these three options to view a box plot graph in a separate window. The example that follows shows raw values.



The graph includes the following:

- The main graph shows the distribution of subjects' lab values as a box plot at each visit along the x-axis.
- An area to the right of the main graph shows box plots of the minimum and maximum normalized values, change from baseline values, or raw values across visits (possibly including visits not represented in the main graph, depending on settings of graph configuration options).
- Counts of subjects with results for the lab test at each visit are shown below the main graph.

In each box plot, the box represents the middle 50% or so of the numeric values. A horizontal line within the rectangle represents the median of all values (that is, the value that is exactly in the middle

of all values). The area above the top end of the box represents the upper quartile, and the area below the bottom end of the box represents the lower quartile. The interquartile range, which is the difference between the upper quartile and the lower quartile, is a measure of the spread of the distribution. The relative distances of the upper and lower quartiles from the median describe the shape of the distribution of data.

The whisker above the box plot extends from the upper quartile to the highest actual value that is within the (75th percentile + 1.5 * (interquartile range)). The whisker below the box plot extends from the lower quartile to the lowest actual value that is within the (25th percentile - 1.5 * (interquartile range)). Outliers are plotted as individual points in the graph. An outlier is considered to be a value that falls outside of the whiskers.

2. When you point to a region of the graph, the following information appears:
   - The region of the box (Upper Outlier, Upper Whisker, Upper Box, Lower Box, Lower Whisker. or Lower Outlier)
   - The count of data points for the visit number and box plot region (only one lab test value is counted per subject and visit number)
3. Click **Configure** to configure the graph. Click **Help** for information about the available configuration options.
4. If the graph is configured to include links, the box plot regions, whiskers, and outlier points are hyperlinks that you can click to drill down to view subject details.

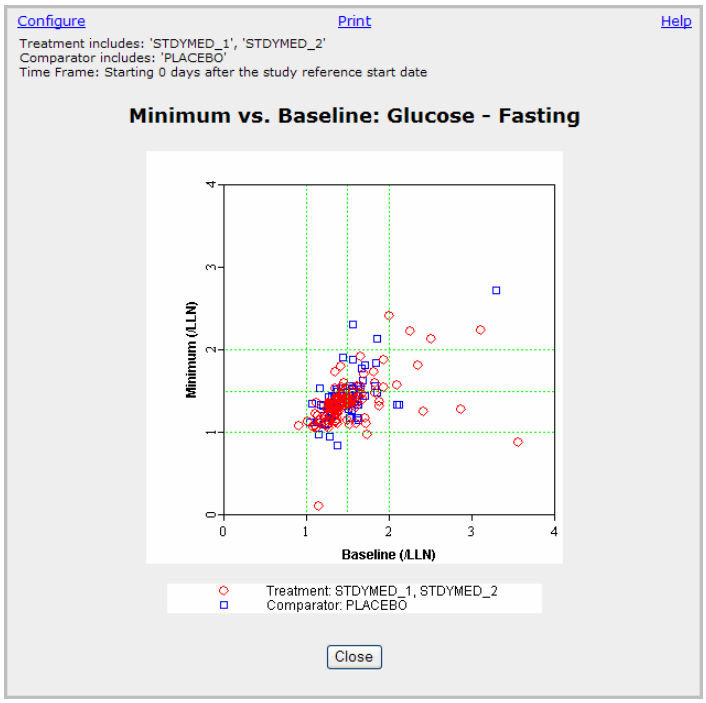
4.4 Lab Change from Baseline

To view a scatter plot showing change from baseline for a lab test:

1. On the Lab Results page, click  for a lab test and then click **Scatter Plot: Shift from Baseline**. This option has two suboptions:

   - **Minimum vs. Baseline**: divides results by the lower limit of normal
   - **Maximum vs. Baseline**: divides results by the upper limit of normal

   Select either of these options to view a scatterplot graph in a separate window. The example that follows shows minimum vs. baseline:



   The graph provides a way to identify shifts in post-baseline lab results relative to baseline values for subjects in the Treatment and Comparator categories. The x-axis represents normalized baseline lab values and the y-axis represents normalized minimum or maximum post-baseline lab values.

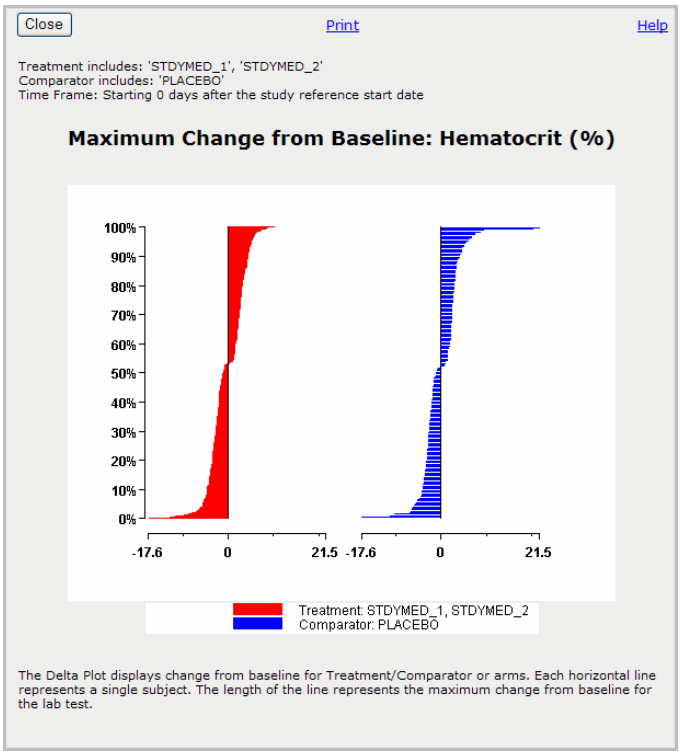
   If a result does not have a lower limit of normal (LLN) or upper limit of normal (ULN), it is omitted from the graph. If no results for a test have an LLN or ULN, actual data values are plotted.

2. As with other graphs, you can drill down to subjects as described in Section 7.1. However, an additional method of drilling down is available for scatter plots. You can click on the graph and drag the mouse to draw a rectangle around several data points. When you release the mouse button, the drilldown menu appears and you can drill down on all of the points within the rectangle.

3. Click **Configure** to configure the graph. Click **Help** for information about the available configuration options.

To view a delta plot showing change from baseline for a lab test:

1. On the Lab Results page, click  for a lab test and then click **Delta Plot: Change from Baseline**. The graph appears in a separate window.



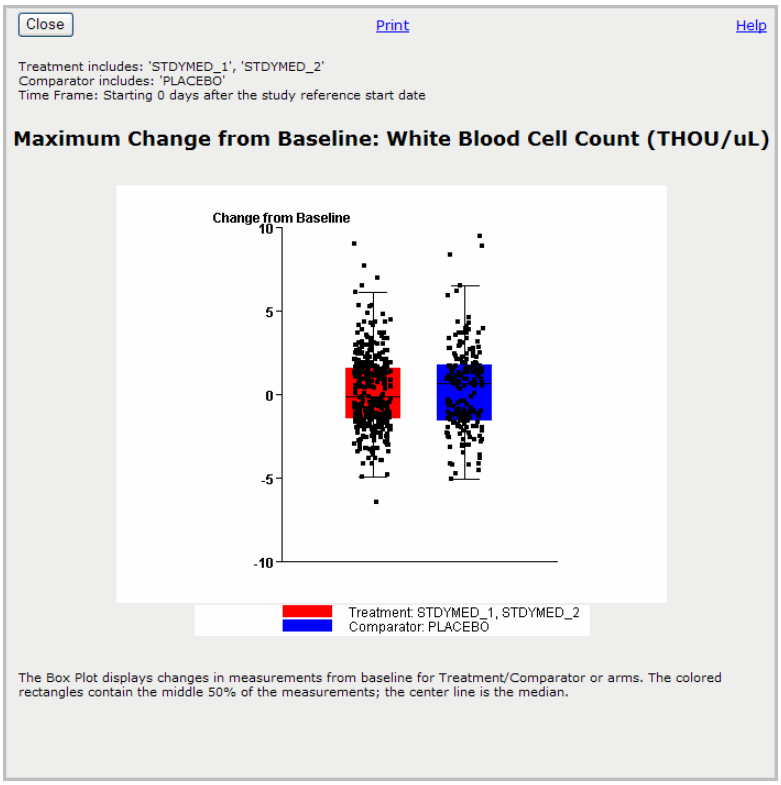
The delta plot compares changes from baseline lab test values for the Treatment and Comparator categories. In a delta plot:

- The x-axis ranges from the lowest change from baseline to the highest change from baseline across all subjects.
- Each line represents the change from baseline for a single subject. (If there is a large number of subjects, lines may appear on top of each other because of space limitations.)
- Each plot is divided into decile regions along the y-axis.

2. If you point to a decile region of the graph, the number of the decile and a count of data points for that decile appear. The count may be more than the number of subjects because the same test may be performed for the same subject more than once; each lab test result is a separate data point.

To view a box plot showing lab change from baseline:

1. On the Lab Results page, click  for a lab test and then click **Box Plot: Change from Baseline**. The graph appears in a separate window.



   The graph shows changes in lab test values from baseline results for the Treatment and Comparator categories. For information about interpreting a box plot, see Section 4.3.

2. If you point to a region of the graph, the region of the box and a count of data points for that region appear.

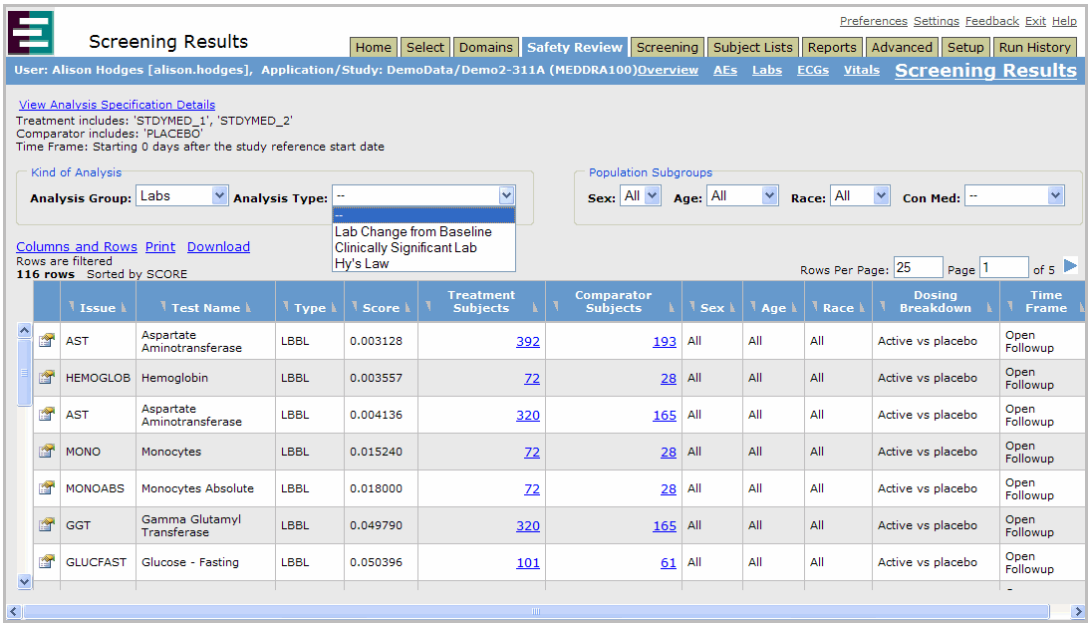
   The count may be more than the number of subjects because the same test may be performed for the same subject more than once; each lab test result would be a separate data point.

4.5 Relationship of Lab Results to Study Drug

Lab screening results provide information about the occurrence of clinically significant lab values, about lab value differences from baseline between Treatment and Comparator categories, and about test values meeting criteria for Hy's Law and liver function tests of critical concern.

To review lab screening results:

1. On the Lab Results page, click **Lab Screening Results**. The Screening Results page appears.
2. In the Analysis Group field, Labs is selected by default since you used the **Lab Screening Results** link to navigate to this page. In the Analysis Type field, you can select a type of lab analysis or "--"to include all results in the table.



3. At the top of the page, the Population Subgroups section offers a field for each category breakdown that was used in the analysis specification that generated the screening analysis results. For example, there may be fields for Sex, Age, and Race. You can limit the results shown in the table to a subgroup by selecting a category value.

   The following tables describe some of the columns available for lab screening analysis results. To display a description of any column, use the mouse to hover the cursor over the column heading

For a Clinically Significant Lab analysis or Hy's Law analysis:

Column	Description
Issue	For a Clinically Significant Lab Analysis, the post-baseline lab results that meet the clinical significance criteria described in Section 7.2. For a Hy's Law Analysis, one of the following: • (ALT or AST) >= 3x ULN, BILI >= 2x ULN, ALP <= 2x ULN • (ALT or AST) >= 3x ULN, BILI >= 1.5x ULN, ALP <= 2x ULN • (ALT or AST) >= 3x ULN, BILI >= 1.5x ULN • (ALT or AST) >= 20x ULN • (ALT or AST) >= 10x ULN • (ALT or AST) >= 5x ULN • (ALT or AST) >= 3x ULN
Test Name or TYPE	For a Clinically Significant Lab Analysis, this column is Test Name and displays the name of the lab test. For a Hy's Law Analysis, this column is Type and displays "LBHY".
Score	One-tailed p-value associated with the chi-statistic. Lower scores are more "interesting".
chi-statistic	The chi-statistic value.
Corrected Odds Ratio	The corrected odds ratio statistic: [(A + 0.5)(D + 0.5)] / [(B + 0.5)(C + 0.5)].
OR025_C	Lower confidence bound of the corrected odds ratio statistic.
A	Count of subjects who received the treatment and experienced the issue within the time frame.
B	Count of subjects who received the comparator and experienced the issue within the time frame.

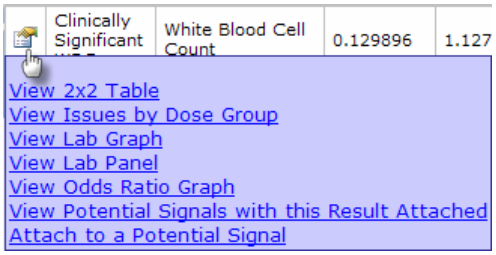
For a Lab Change from Baseline analysis:

Column	Description
Issue	Short name for the lab test.
Test Name	Name of the lab test.
Score	Two-tailed p-value associated with the t-statistic. Lower scores are more "interesting".
t-statistic	The t-statistic value.
Treatment Subjects	Total count of subjects who received the treatment and have sufficient data to determine if the issue occurred.
Comparator Subjects	Total count of subjects who received the comparator and have sufficient data to determine if the issue occurred.
Mean for Treatment	Mean of test change from baseline values for subjects who received the treatment.
Mean for Comparator	Mean of test change from baseline values for subjects who received the comparator.
Std. Deviation for Treatment	Standard deviation of test change from baseline values for subjects who received the treatment.
Std. Deviation for Comparator	Standard deviation of test change from baseline values for subjects who received the comparator.

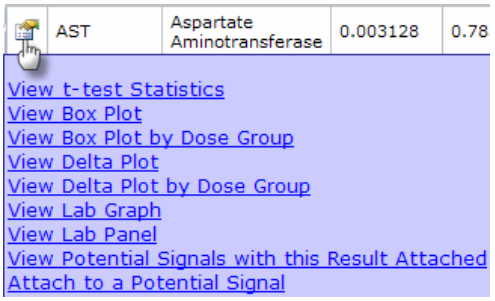
You can click **Columns and Rows** to select columns to display, define the order in which they appear, and specify a sort order. You also have the option to specify a SQL Where clause to filter rows.

To view issues by dose group:

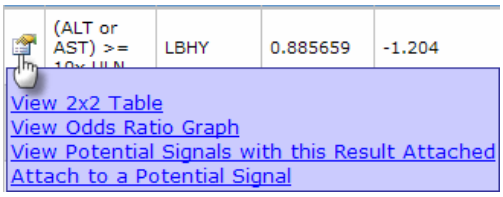
1. On the Lab Screening Results page, if you click for an issue, a menu of options appears. For a Clinically Significant Lab analysis result, the options are:



2. For a Lab Change from Baseline result, the options are:



3. For a Hy's Law result, the options are:



Some of these options are similar to options on the Lab Results page, but they show information for subgroups such as sex and age that were used to generate screening results. For information about using each of these options, see the online help.

4.6 Liver Function Tests (LFTs)

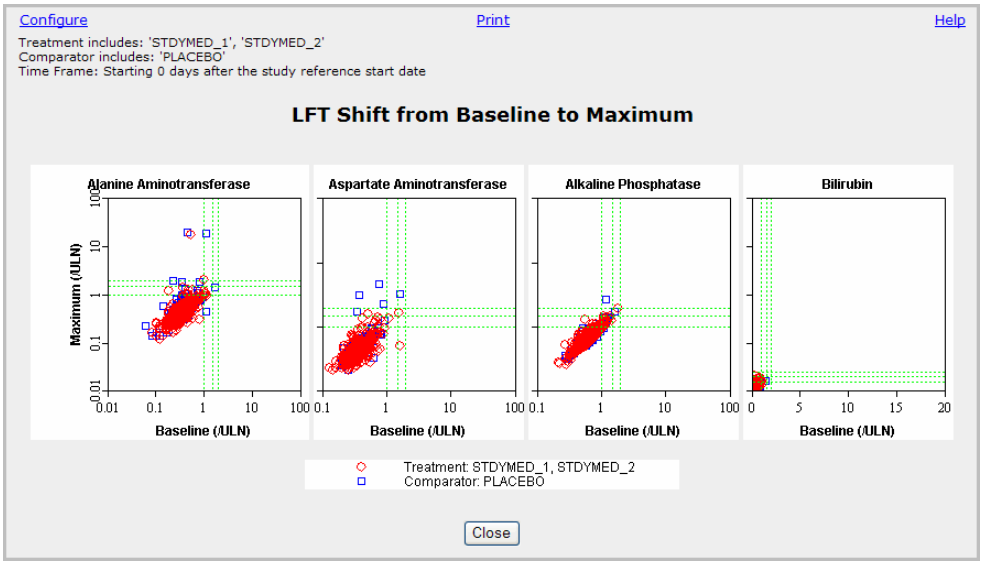
You can produce graphs of results for the following liver function tests (LFTs):

- Alanine Aminotransferase
- Aspartate Aminotransferase
- Alkaline Phosphatase
- Bilirubin

Note: You can view Liver Function Test and other findings profiles for a single subject or a group of subjects as described in Section 7.1.

To review LFT Changes from Baseline:

1. On the Lab Results page, click **LFT Scatter Plots: Shift from Baseline**. The graph appears in a separate window.



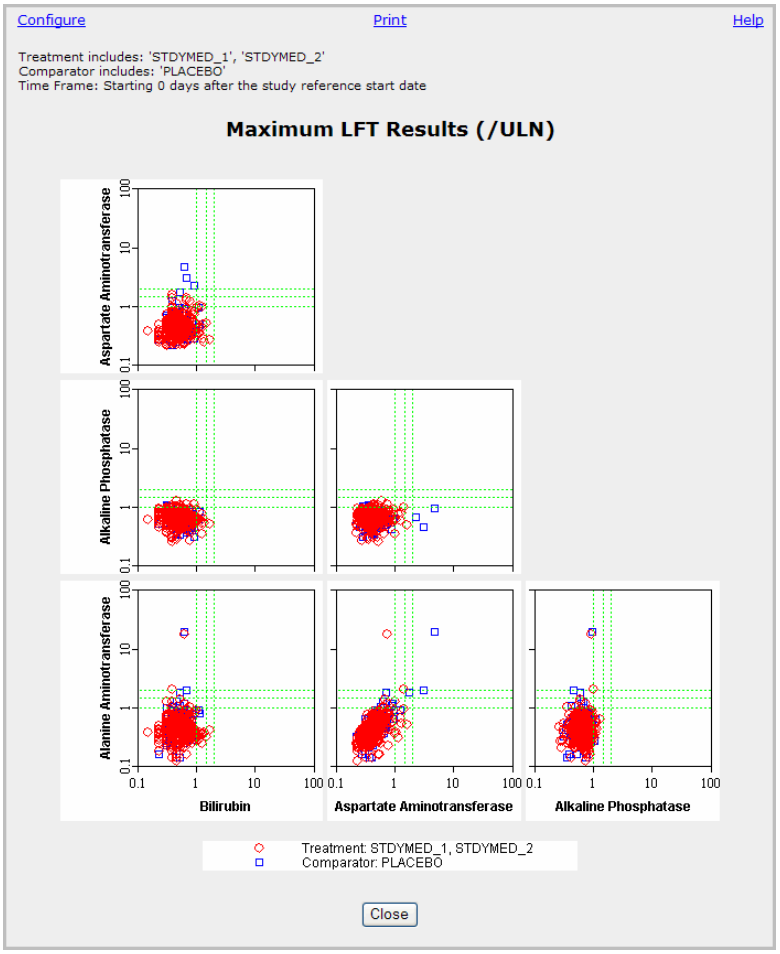
   The graph displays a scatter plot for each of the four liver function tests, providing a way to identify elevations in LFT values relative to baseline LFT values. In each graph, the x-axis represents baseline values and the y-axis represents maximum post-baseline values. The graph plots normalized lab values, that is, lab values divided by the upper limit of normal.

2. Click **Configure** to configure the graph. Click **Help** for information about the available configuration options.

3. As with other graphs, you can drill down to subjects as described in Section 7.1. However, an additional method of drilling down is available for scatter plots. You can click on the graph and drag the mouse to draw a rectangle around several data points within one of the four plots. When you release the mouse button, the drilldown menu appears and you can drill down on all of the points within the rectangle.

To review the relationships between liver function tests:

1. On the Lab Results page, click **LFT Scatter Plot Matrix: Maximum Results**. A scatter plot for each pairwise combination of the four liver function tests appears.



   The Maximum LFT Results graph provides a way to identify maximum post-baseline LFT values that are elevated simultaneously in pairs of liver function tests. A scatter plot appears for each pairwise combination of the four liver function tests. In each scatter plot, the x-axis represents maximum values for one of the liver function tests, and the y-axis represents maximum values for another of the liver function tests. The graph plots normalized lab values, that is, lab values divided by the upper limit of normal.

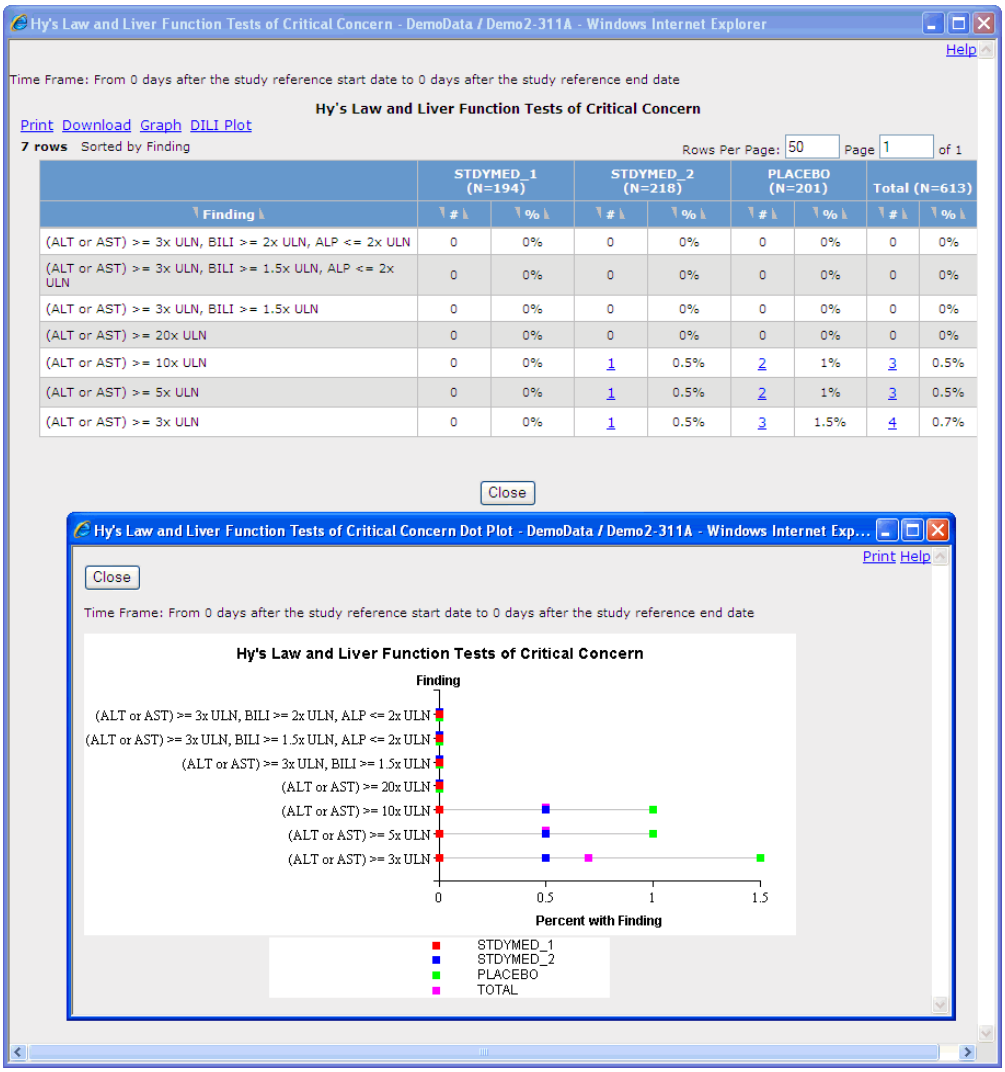
2. Click **Configure** to configure the graph. Click **Help** for information about the available configuration options.

3. You can work with the scatter plots in this matrix in the same way that you work with an individual scatter plot showing change from baseline. Additionally, when you click one of the scatter plots, you can then click **Zoom** to display an enlarged version of that scatter plot in its own window.

To review a summary of Hy's Law and liver function tests of critical concern:

1. On the Lab Results page, click **Hy's Law**. A table of post-baseline results for the ALT, AST, BILI, and ALP tests appears in a separate window. The summary displays counts and percentages of subjects with each of the findings.

2. To display the information graphically, click **Graph**. A dot plot showing the percentage of subjects with each finding appears.



Finding	STDYMED_1 (N=194) #	STDYMED_1 (N=194) %	STDYMED_2 (N=218) #	STDYMED_2 (N=218) %	PLACEBO (N=201) #	PLACEBO (N=201) %	Total (N=613) #	Total (N=613) %
(ALT or AST) >= 3x ULN, BILI >= 2x ULN, ALP <= 2x ULN	0	0%	0	0%	0	0%	0	0%
(ALT or AST) >= 3x ULN, BILI >= 1.5x ULN, ALP <= 2x ULN	0	0%	0	0%	0	0%	0	0%
(ALT or AST) >= 3x ULN, BILI >= 1.5x ULN	0	0%	0	0%	0	0%	0	0%
(ALT or AST) >= 20x ULN	0	0%	0	0%	0	0%	0	0%
(ALT or AST) >= 10x ULN	0	0%	1	0.5%	2	1%	3	0.5%
(ALT or AST) >= 5x ULN	0	0%	1	0.5%	2	1%	3	0.5%
(ALT or AST) >= 3x ULN	0	0%	1	0.5%	3	1.5%	4	0.7%

3. You may want to drill down on subjects as described in Section 7.1, and display an LFT Patient Profile, which shows details about liver function tests for particular subjects.

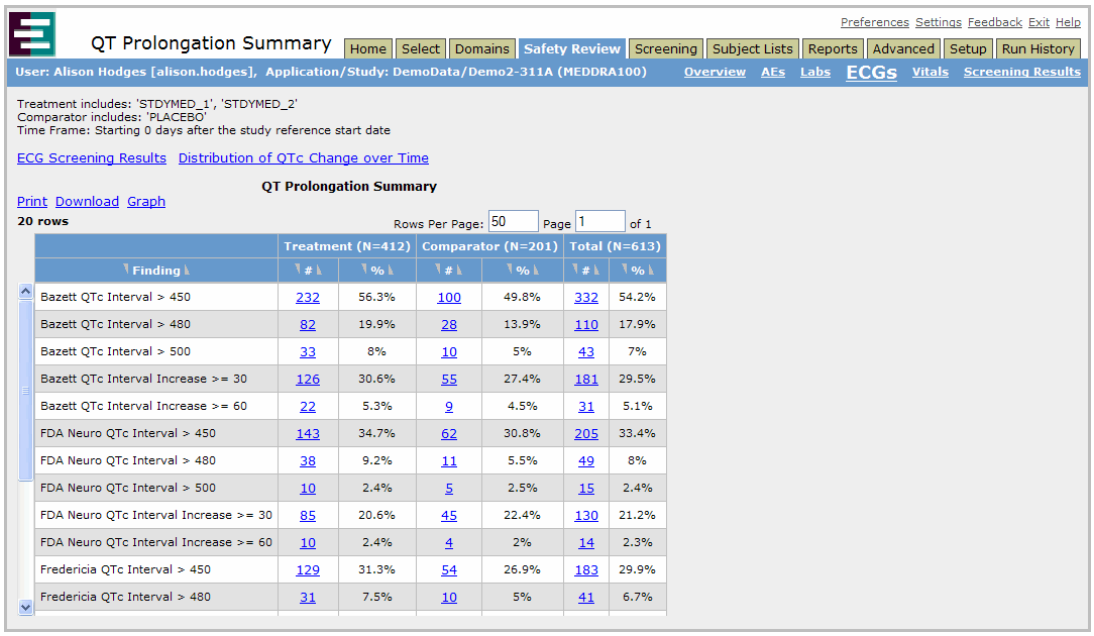
4. You can also view the Drug-Induced Liver Injury (DILI) plot. Click the **DILI Plot** link on the Hy's Law and Liver Function Tests of Critical Concern page.

5 Reviewing ECG Results

To review ECG results:

1. On the Safety Review tab, click **ECGs**. The QT Prolongation Summary page appears.

   Note: A message may inform you that the issue list needs to be updated. If you click **OK**, the Run Options page appears so that you can specify options for executing an "automatic screening run". This run generates the list of issues that may appear in the QT Prolongation Summary.



Finding	Treatment (N=412) #	Treatment (N=412) %	Comparator (N=201) #	Comparator (N=201) %	Total (N=613) #	Total (N=613) %
Bazett QTc Interval > 450	232	56.3%	100	49.8%	332	54.2%
Bazett QTc Interval > 480	82	19.9%	28	13.9%	110	17.9%
Bazett QTc Interval > 500	33	8%	10	5%	43	7%
Bazett QTc Interval Increase >= 30	126	30.6%	55	27.4%	181	29.5%
Bazett QTc Interval Increase >= 60	22	5.3%	9	4.5%	31	5.1%
FDA Neuro QTc Interval > 450	143	34.7%	62	30.8%	205	33.4%
FDA Neuro QTc Interval > 480	38	9.2%	11	5.5%	49	8%
FDA Neuro QTc Interval > 500	10	2.4%	5	2.5%	15	2.4%
FDA Neuro QTc Interval Increase >= 30	85	20.6%	45	22.4%	130	21.2%
FDA Neuro QTc Interval Increase >= 60	10	2.4%	4	2%	14	2.3%
Fredericia QTc Interval > 450	129	31.3%	54	26.9%	183	29.9%
Fredericia QTc Interval > 480	31	7.5%	10	5%	41	6.7%

This table provides counts and percentages for findings about QTc intervals. The QTc intervals are either as reported in the study data, or are computed using the following correction methods:

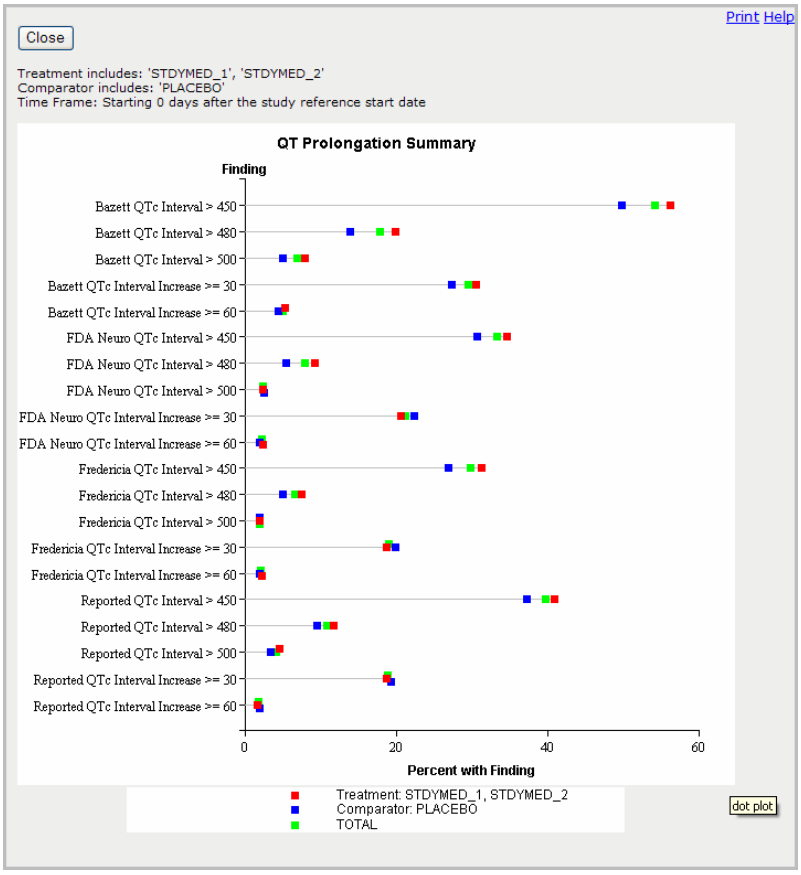
- Bazett's formula = QTmsec / (RR sec)$^{0.5}$
- FDA Neuropharmacological Division's formula = QTmsec / (RR sec)$^{0.37}$
- Fredericia's formula = QTmsec / (RR sec)$^{0.33}$

Possible findings are as follows:

- <*correction-method*> QTc Interval > 450
- <*correction-method*> QTc Interval > 480
- <*correction-method*> QTc Interval > 500
- <*correction-method*> QTc Interval Increase >= 30
- <*correction-method*> QTc Interval Increase >= 60

where <*correction-method*> is Reported, Bazett, FDA Neuro, or Fredericia.

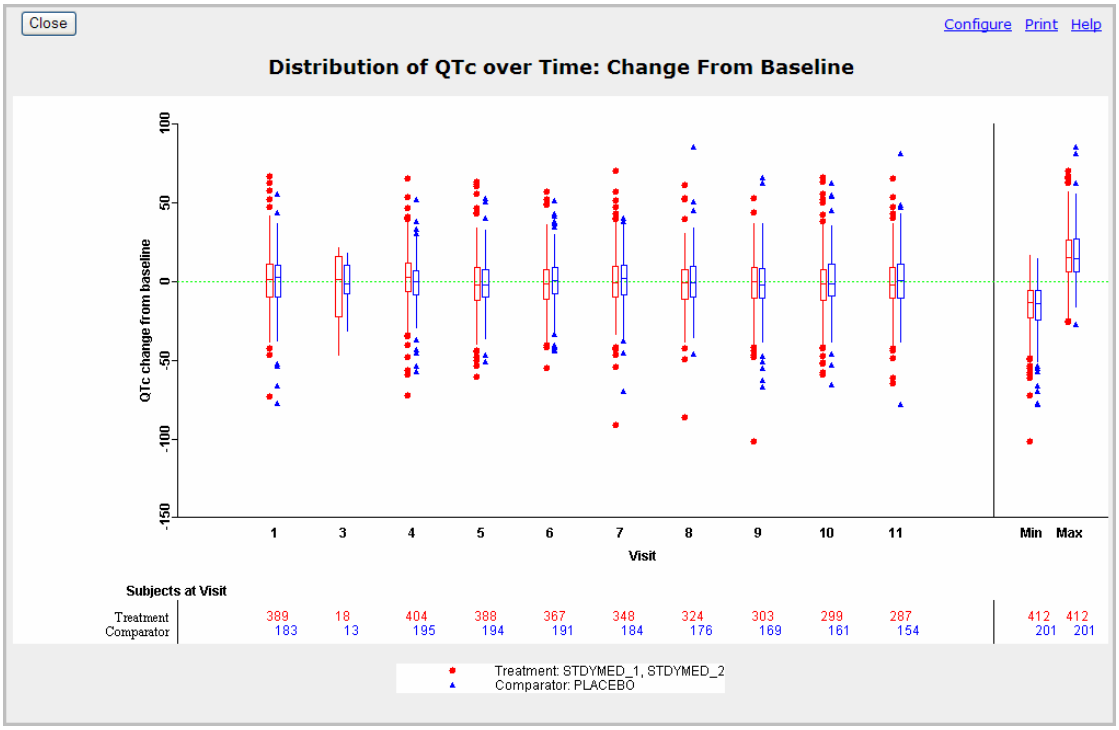
2. To view a graph of the incidence of the above QTc intervals, click **Graph**. A dot plot appears in a separate window.



5.1 QTc Interval Change from Baseline

To view QTc Interval Change from Baseline:

1. On the QT Prolongation Summary page, click **Distribution of QTc Change over Time.** A box plot appears in a separate window.



   The graph provides the following information for subjects in the Treatment and Comparator categories:

   - The main graph shows the distribution of changes from baseline in reported QTc interval values as a box plot at each visit along the x-axis.
   - An area to the right of the main graph shows box plots of the maximum reported QTc interval changes from baseline across all visits (possibly including visits not represented in the main graph, depending on settings of graph configuration options). Maximum values are the largest differences from baseline, where positive differences are always larger than negative differences.
   - Counts of subjects with reported QTc interval changes from baseline at each visit are shown below the main graph.

   For information about interpreting box plots, see Section 4.3.

2. Click **Configure** to configure the graph. Click **Help** for information about the available configuration options.

3. When you point to a region of the graph, the following information appears:

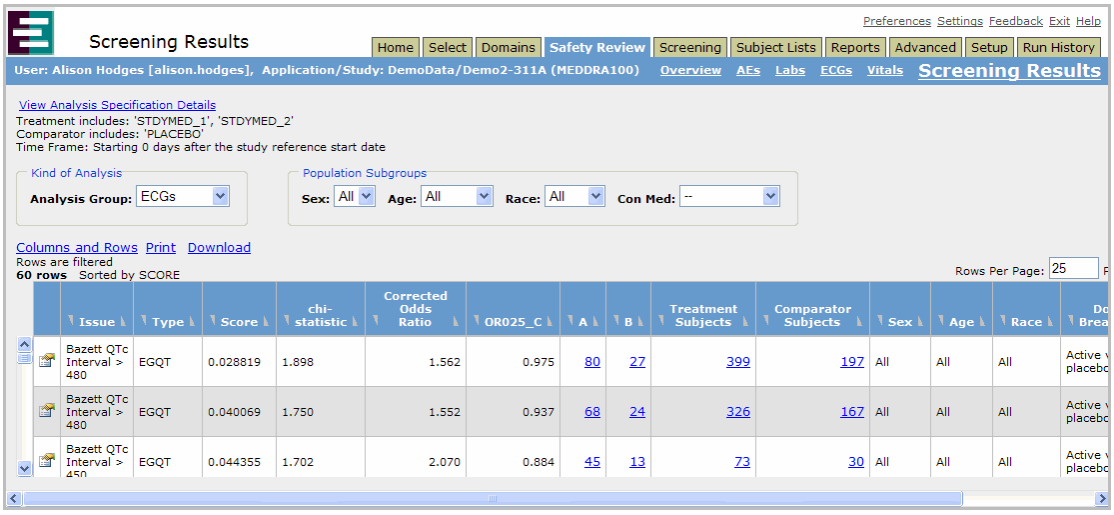
   - The region of the box (Upper Outlier, Upper Whisker, Upper Box, Lower Box, Lower Whisker. or Lower Outlier)
   - The count of data points for the visit number and box plot region (only one QTc interval value is counted per subject and visit number)

4. If the graph is configured to include links, the box plot regions, whiskers, and outlier points are hyperlinks that you can click to drill down to view subject details.

5.2 Relationship of ECG Results to Study Drug

To review the relationship of ECG results to the study drug:

1. On the QT Prolongation Summary page, click **ECG Screening Results**. The Screening Results page appears with the Analysis Group set to ECGs by default.



You work with ECG screening results in the same way you work with lab screening results, described in Section 4.5. There is no Analysis Type field on the ECG Screening Results page because there is only one analysis type, the QT Interval Prolongation Analysis.

The following table describes some of the columns that you can use to view these analysis results. You can also hover over a column heading to display a description of the column.

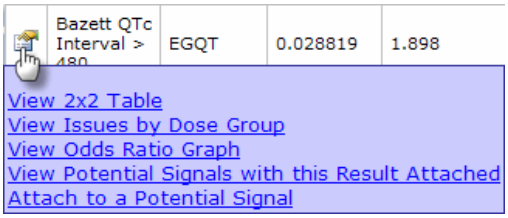
Column	Description
Issue	One of the following: • <*correction-method* QTc Interval > 450 • <*correction-method* QTc Interval > 480 • <*correction-method* QTc Interval > 500 • <*correction-method* QTc Interval Increase >= 30 • <*correction-method* QTc Interval Increase >= 60 where <*correction-method* is Reported, Bazett's, FDA Neuro, or Fredericia's.
Type	EGQT, an abbreviation of the type of analysis, which is a QT Interval Prolongation Analysis.
Score	One-tailed p-value associated with the chi-statistic. Lower scores are more “interesting”.
chi-statistic	The chi-statistic value.
Corrected Odds Ratio	The corrected odds ratio statistic: [(A + 0.5)(D + 0.5)] / [(B + 0.5)(C + 0.5)].
OR025_C	Lower confidence bound of the corrected odds ratio statistic.

Column	Description
A	Count of subjects who received the treatment and experienced the issue within the timeframe.
B	Count of subjects who received the comparator and experienced the issue within the timeframe.
Treatment Subjects	Total count of subjects who received the treatment and have sufficient data to determine if the issue occurred.
Comparator Subjects	Total count of subjects who received the comparator and have sufficient data to determine if the issue occurred.

You can click **Columns and Rows** to select columns to display, define the order in which they appear, and specify a sort order. You also have the option to specify a SQL Where clause to filter rows.

To view issues by dose group:

On the ECG Screening Results page, if you click for an issue, a menu of options appears:

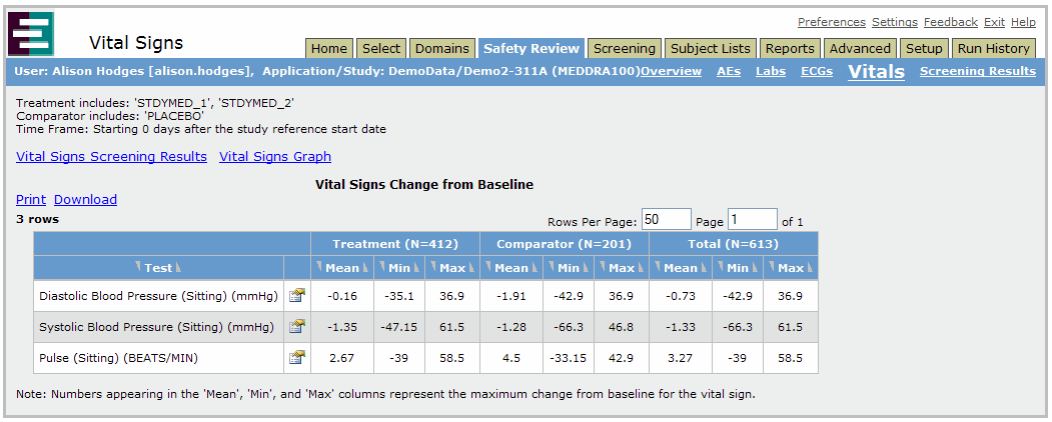


For information about using these options, see the online help.

6 Reviewing Vital Signs Results

To review vital sign results:

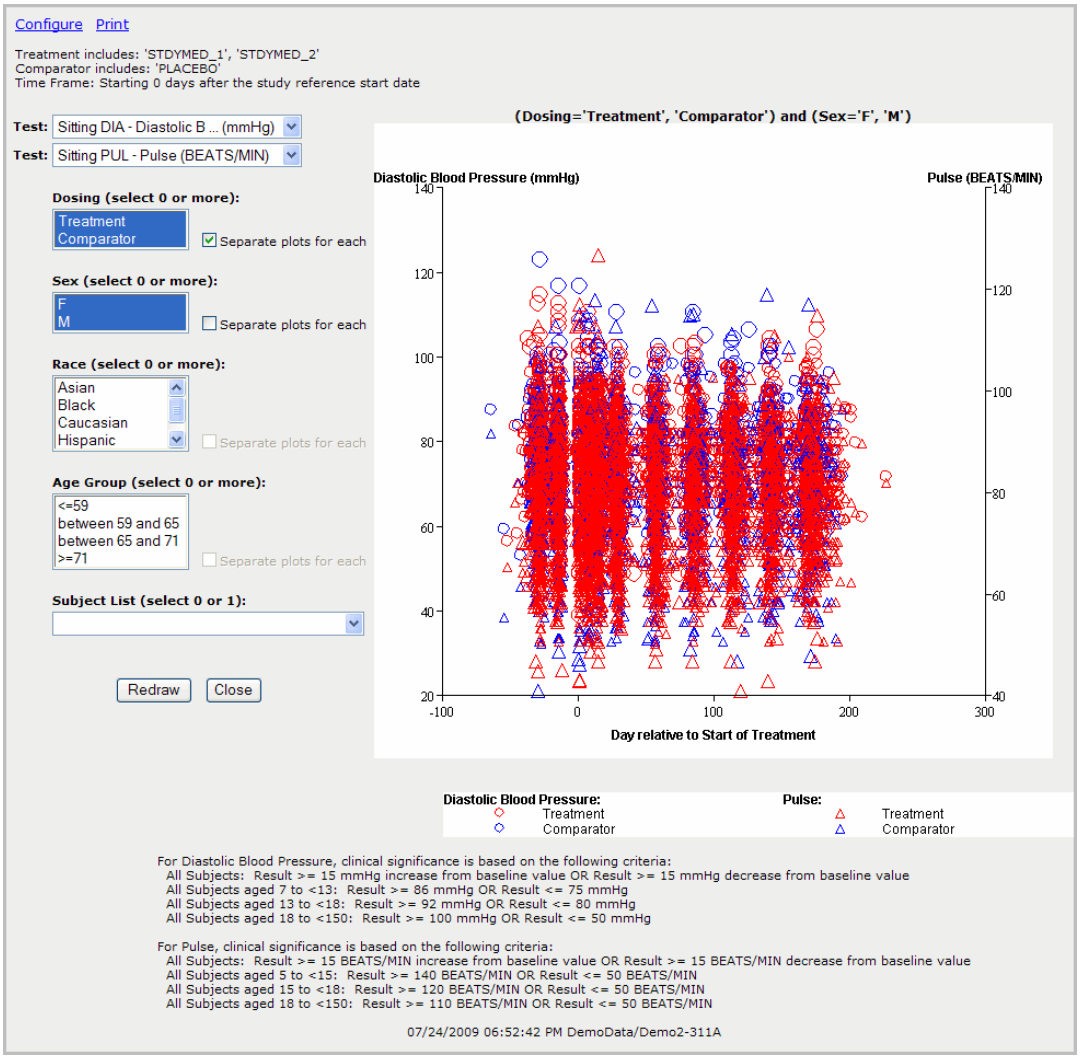
1. On the Safety Review tab, click **Vitals**. The Vital Signs page appears.



   The Vital Signs page displays change from baseline information for vital signs data in the study. The table includes one row for each combination of the long name of the vital sign and position, if any. The position appears in parentheses, followed by the result units in parentheses. The mean value, the minimum value, and the maximum value of change from baseline are reported for each vital sign.

2. You can click  for a vital sign to select the same options for a vital signs test as are described for lab tests in Sections 4.2 through 4.4.

3. To view a graph of results from individual vital signs tests click **Vital Signs Graph**. One or two vital signs can be plotted by the graph.

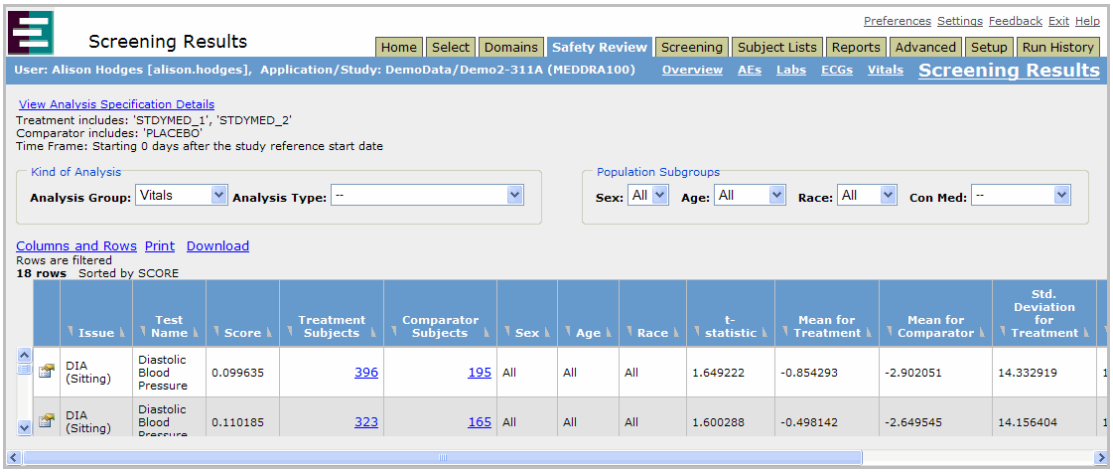


The options for this graph are similar to those described in Section 4.1, Lab Results for Subgroups.

To review the relationship of vital sign results to the study drug:

Vital signs screening results provide information about the occurrence of clinically significant vital sign values and about vital sign value differences from baseline between Treatment and Comparator categories.

1. On the Vital Signs page, click **Vital Signs Screening Results**. The Screening Results page appears with the Vitals Analysis Group selected by default.



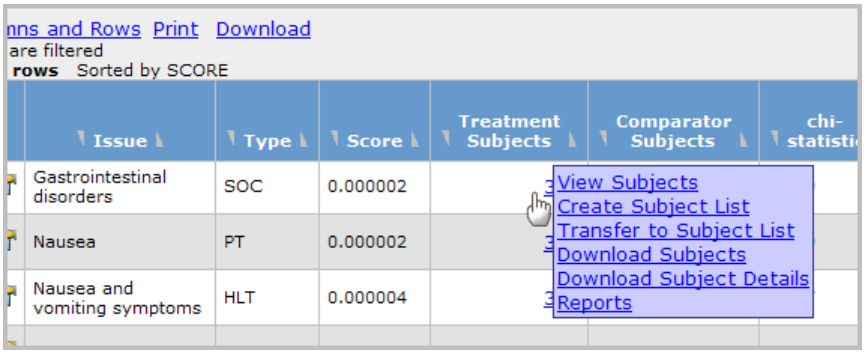
2. You work with vital signs screening results in the same way you work with lab screening results, described in Section 4.5. Available analysis types are Clinically Significant Vitals and Vitals Change from Baseline. Clinical significance criteria are described in Section 7.3.

7 Appendices

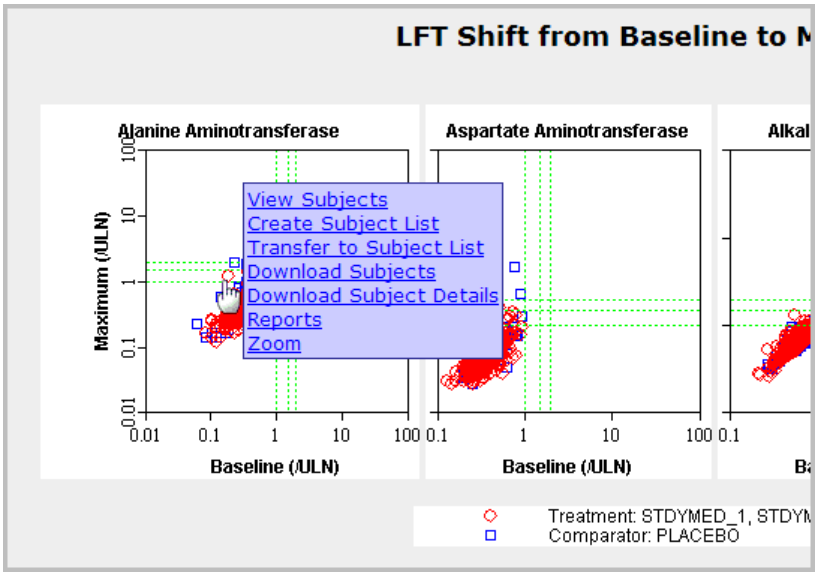
7.1 Drilling Down to Subject Details

To drill down on a subject count:

On the Safety Review tab, when a hyperlinked count of subjects appears in a table you can click that count to display the following menu of options:



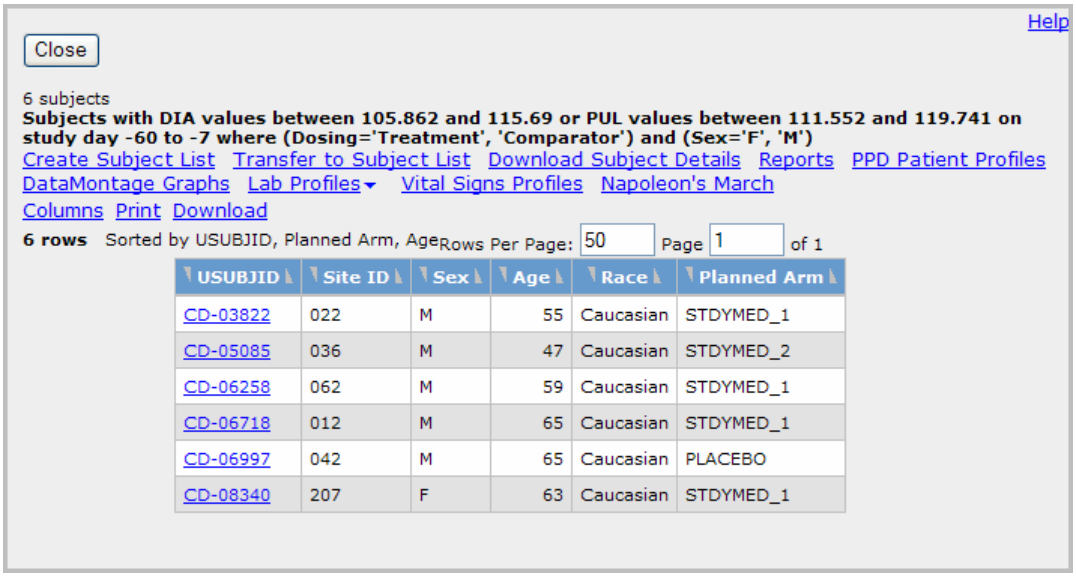
You can also click on an element (such as a dot or bar) in a Safety Review graph:



(Some graphs also offer a Zoom option to allow you to see a larger image of the current graph.)

This is called the “drilldown menu” and its options act on the subjects comprising the count.

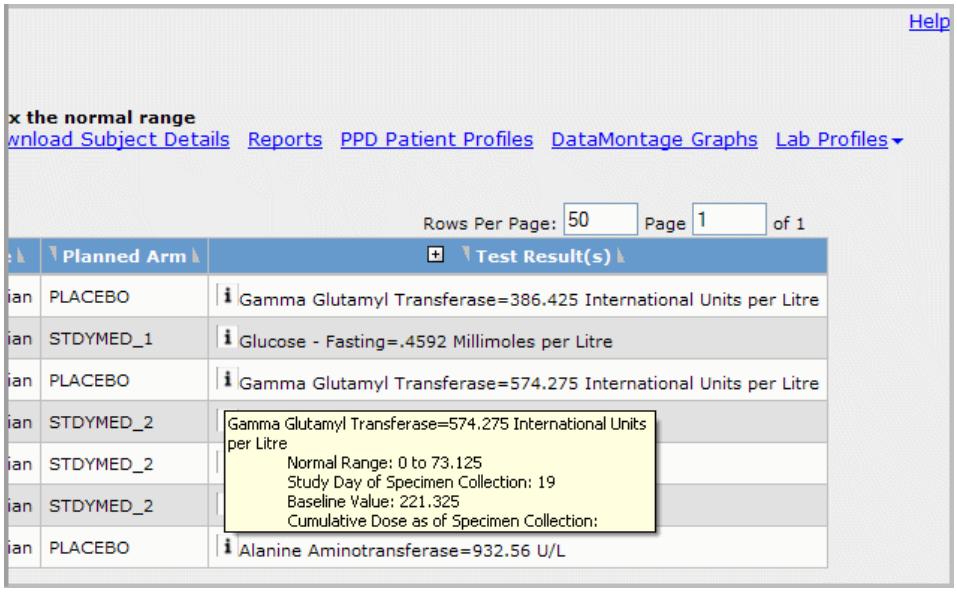
For example, you can click **View Subjects** to display a list of the subjects that comprise a count:



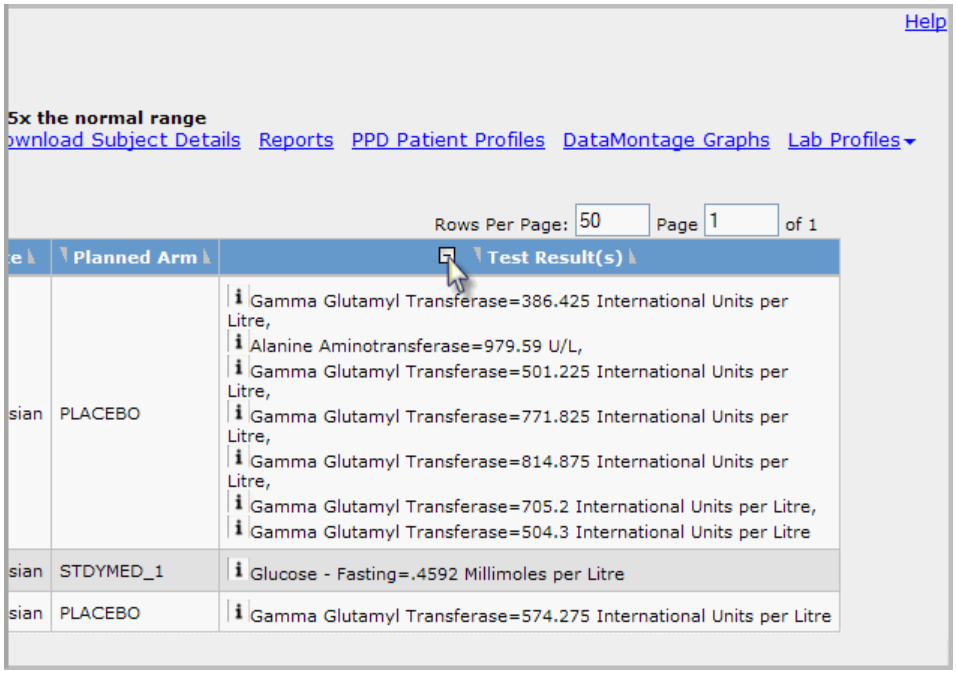
This Subjects page is sometimes referred to as "first level drilldown", and offers a number of options for investigating subject data in addition to the displayed table of subject information.

In some contexts, the table on the Subjects page includes an extra column, such as the Test Result(s) column in the following example. When present, this extra column offers the following features:

- If an informational "i" symbol appears before a value in this column you can hover the cursor over it to display additional information.

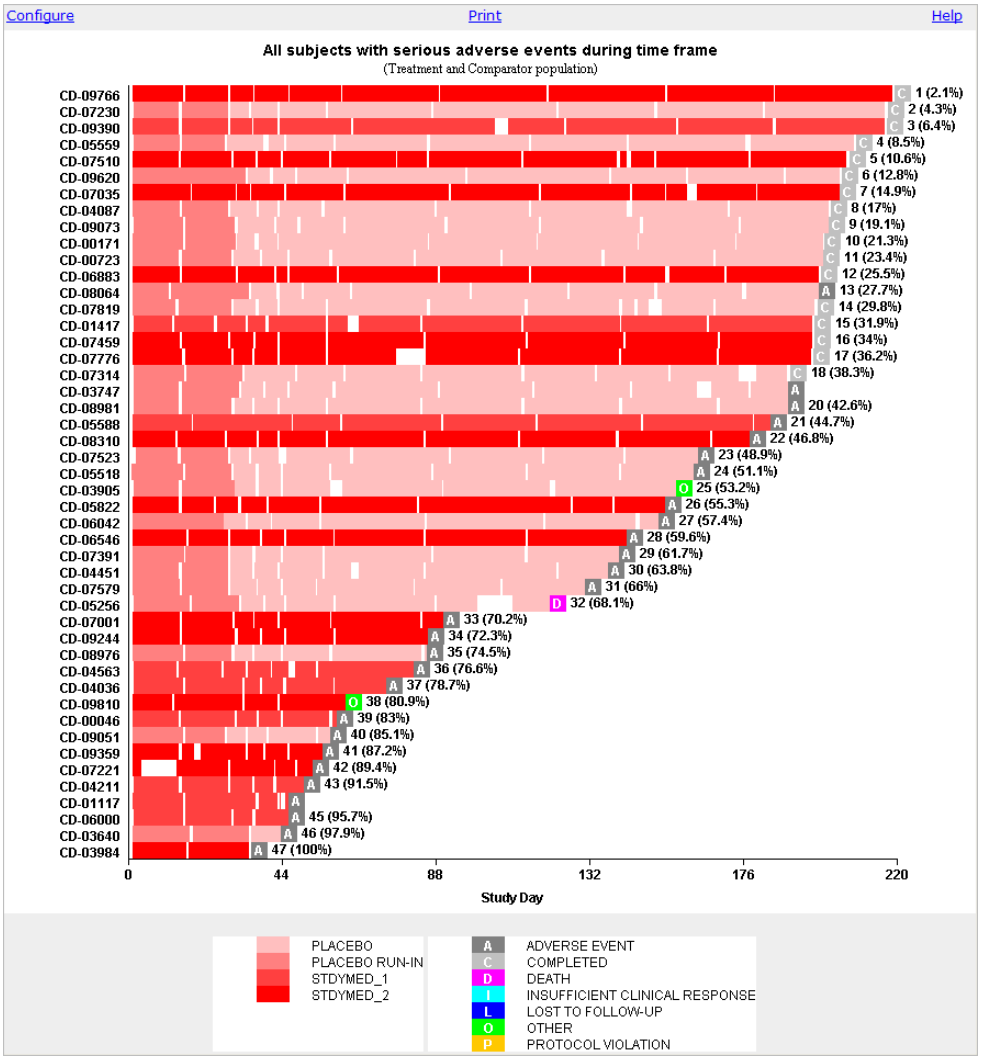


- You can click the "+" symbol in the column header to expand each row and show information about all applicable values of this type for the subject.



To view reasons for study termination:

1. On the Subjects page, click **Napoleon's March**. The graph can be displayed only if there are 500 or fewer subjects to be represented in the graph. Do not click on the graph until the whole graph appears.



A Napoleon's March graph provides information about subject exposure to treatment during the study, adverse events experienced by subjects, and the circumstances under which subjects completed or dropped out of the study. The temporal relationship between duration of exposure and the onset of an adverse event can be important in assessing causality. For example, a rare but serious adverse event that occurs more frequently in the treatment group might also occur earlier in the treatment group and be more likely in the treatment group to lead to dropout.

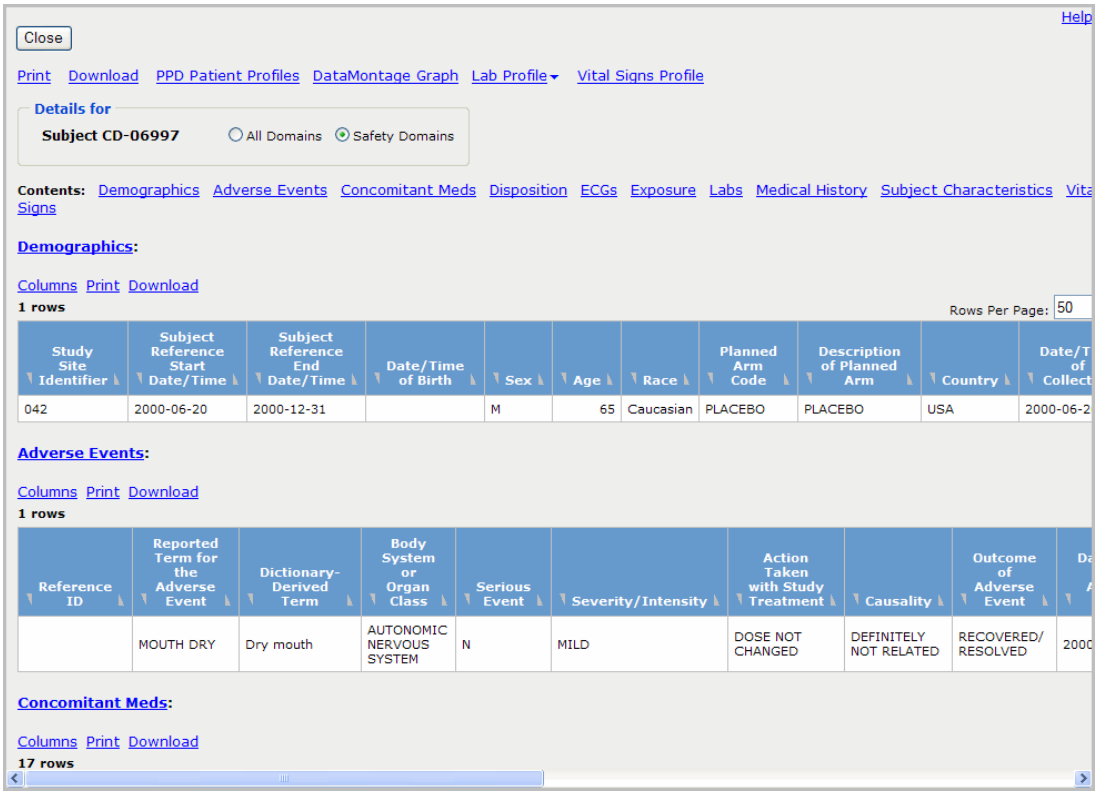
2. Click **Configure** to configure the graph. For example, you can graph subjects in the Treatment and Comparator categories separately for a side by side comparison. Click **Help** for information about the available configuration options.

3. When you point to a bar in the graph, the subject's ID, sex, age, arm, and disposition appear.

4. To drill down a second time to information for a specific subject, click a bar (after the whole graph has displayed). The Subject Details page appears.

To view subject details:

On the Subjects page (and also from the Napoleon's March graph), you can click a particular subject ID to drill down further to details for the subject:



These subject details are sometimes referred to as "second level drilldown", and provide access to the actual data reported for a subject.

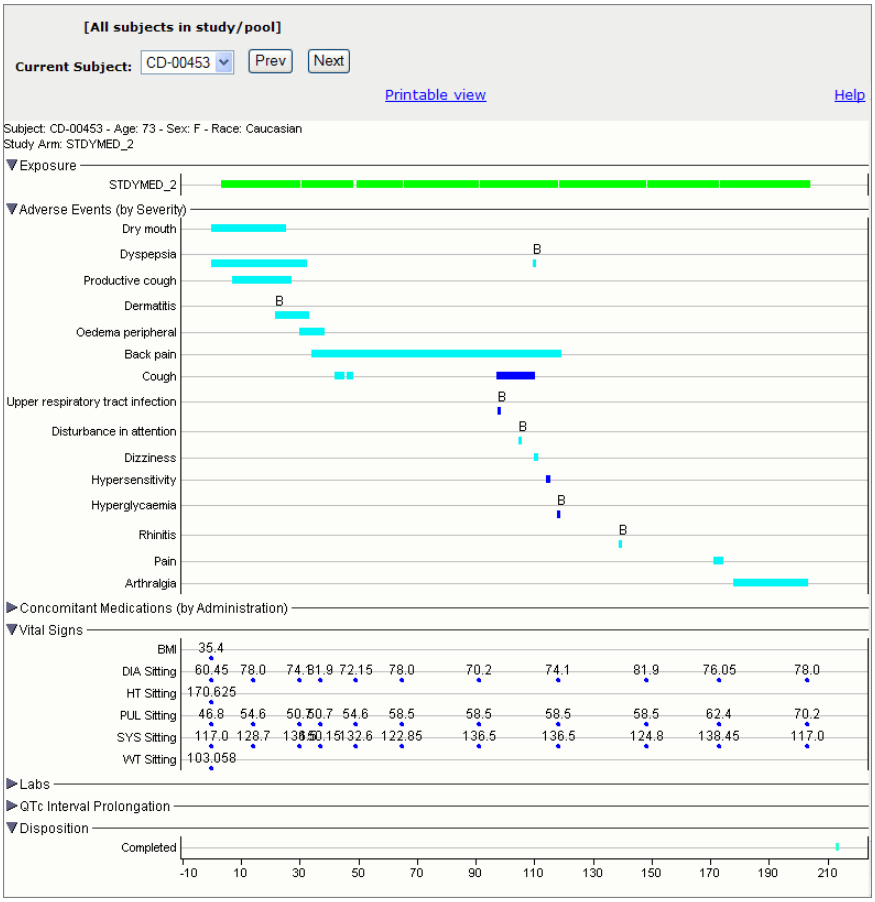
To view subject details graphically:

DataMontage™ is a third-party application that enables you to view graphical displays of individual subjects' data using timelines. A DataMontage graph shows data by domain. The y-axis represents interventions, events, or findings such as adverse events or lab tests, and the x-axis represents study days. For all domains except Vital Signs, QTc Intervals, and Labs, a horizontal bar shows duration; for those domains, points on the graph show when tests occurred as well as the test values.

You can produce the graph for the single subject shown on the second level drilldown Subject Details page. You can also produce a set of graphs for each of the subjects on the first level drilldown Subjects page.

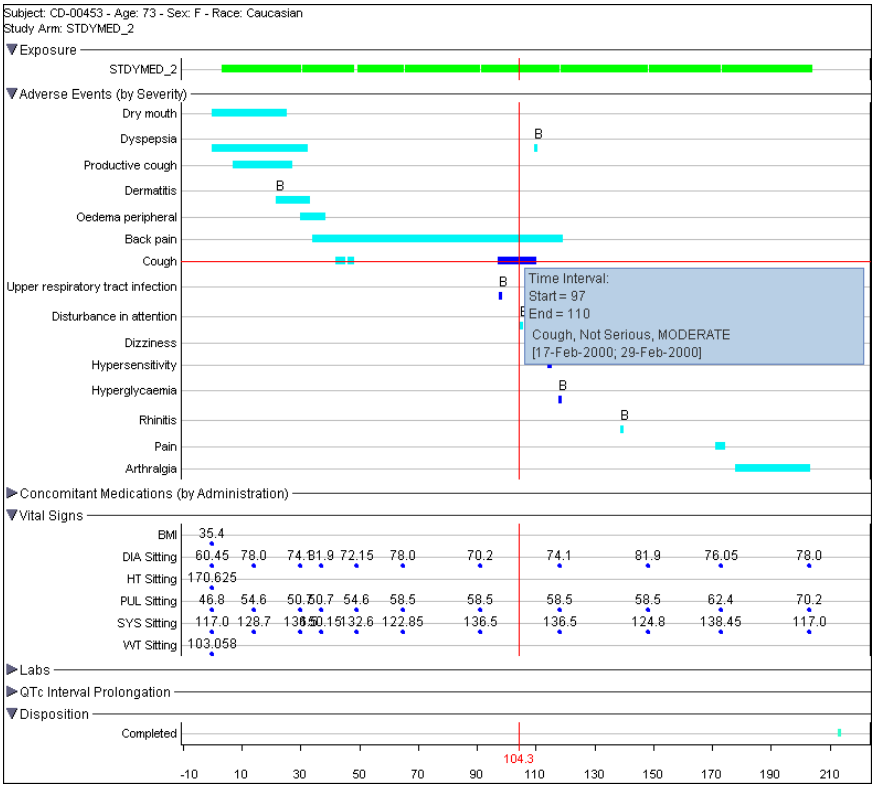
Note: If the graph does not appear as you follow these instructions, click **Preferences** in the main Empirica Study window to check the setting for the "Run DataMontage as applet" preference. If you plan to use DataMontage interactively, you must install a JRE for DataMontage on your computer (see Prerequisites and Usage Notes in the online help). If you have not yet installed the JRE, the checkbox for this preference must be cleared so that a static JPEG image can be produced instead.

1. On the Subject Details page click **DataMontage Graph**. Alternatively, on the Subjects page, click **DataMontage Graphs**. The graph (or first in the set of graphs) appears in a separate window.



This example was produced from the Subjects page and shows the controls that are available above the graph to select each subject in the list.

2. If you are running DataMontage as an applet, you can click on the graph to set reference lines, or hover the mouse over an element to view details about it.



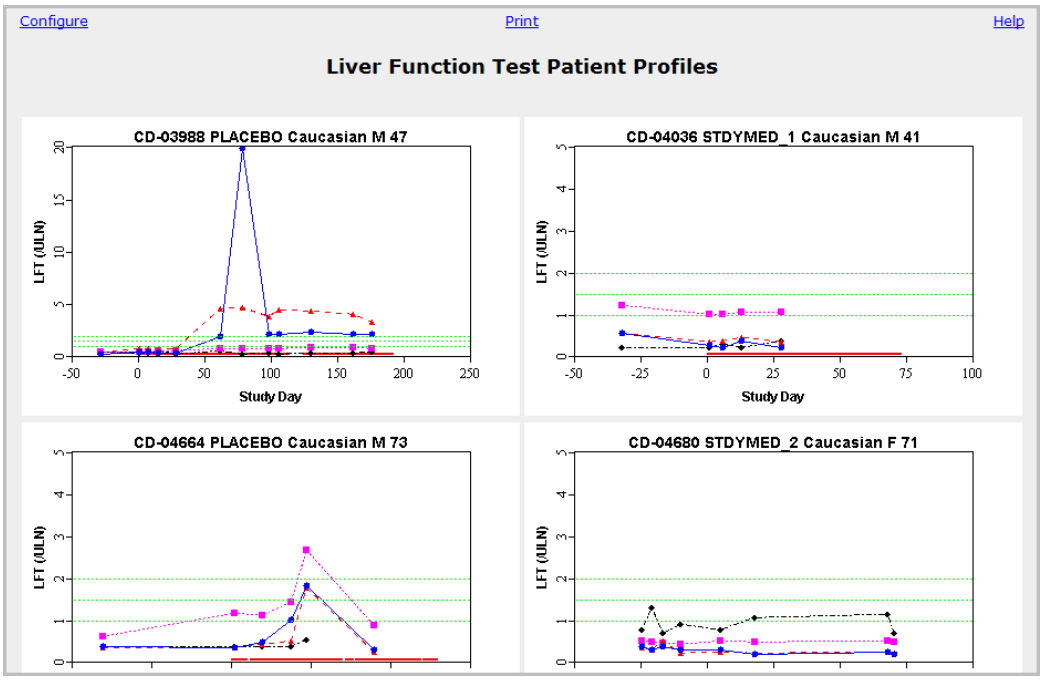
To collapse a section (domain) of the graph, click the down arrow before the section label. To expand a section of the graph, click the right arrow before the section label. If you have expanded all sections, you may need to scroll down to see all domains.

For further instructions on using a DataMontage graph, see the online help.

To view graphs of findings data:

You can produce graphs of lab profiles or vital signs profiles when you drill down to a single subject, or produce graphs for all of the subjects on the first level drilldown Subjects page. For example, to produce a Liver Function Test Patient Profile that plots the results of four liver function tests (LFTs) over time:

1. In the Subjects or Subject Details window, click **Lab Profiles** then **Liver Function Tests**. A separate window opens with an LFT graph for every subject in the list or an LFT graph for the single subject:



   This example was produced from the Subjects page and shows a graph for each subject in the list.

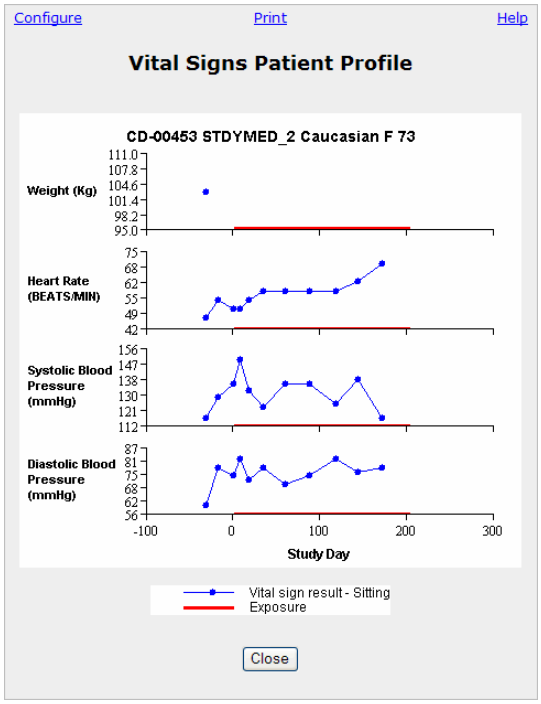
   The graph facilitates identification of LFT value elevations for the subject. The x-axis represents study days, and the y-axis represents normalized LFT values. Each sequential pair of values is connected by a line. Additionally, a red horizontal reference line along the x-axis shows the subject's treatment period, so that you can assess elevated values' temporal relationship to treatment and evaluate the elevation onset and duration.

2. Click **Configure** to configure the graph. Click **Help** for information about the available configuration options.

The options that are available when you click **Lab Profiles** on the Subjects or Subject Details page are:

- **Liver Function Tests**
- **Standard Hematoxicity**
- **Anemia Hematoxicity**
- **Hemolytic Anemia Hemotoxicity**

The **Vital Signs Profile** option produces a set of four graphs that plot the results of four different vital signs over time. Each measurement has its own Y-axis. For example:



The findings plotted by each of these options are:

Profile	Findings Plotted
Liver Function Tests	Alanine Aminotransferase (ALT) Aspartate Aminotransferase (AST) Alkaline Phosphatase (ALP) Bilirubin (BILI)
Standard Hematoxicity	Hemoglobin (HGB) Platelet (PLAT) Neutrophils/Leukocytes (NEUTLE) Leukocytes (WBC)
Anemia Hematoxicity	Reticulocytes (RETI) Hemoglobin (HGB) Erythrocytes (RBC) Ery. Mean Corpuscular Volume (MCV) Ery. Mean Corpuscular HB Concentration (MCHC)
Hemolytic Anemia Hemotoxicity	Hemoglobin (HGB) Bilirubin (BILI) Indirect Bilirubin (BILIND) Lactate Dehydrogenase (LDH) Haptoglobin (HAPTOG)
Vital Signs Profile	Weight (WEIGHT) Heart Rate (HR) Systolic Blood Pressure (SYSBP) Diastolic Blood Pressure (DIABP)

For more information on patient profile graphs for findings, see the online help.

7.2 Clinically Significant Lab Values

Clinical significance for lab tests or vital signs may be determined according to built-in criteria supplied with Empirica Study or according to a study data variable designated when the study is set up. The following built-in criteria are used to determine whether a lab test result is clinically significant in a Clinically Significant Lab analysis shown on the Screening Results page.

Note: The following criteria are *not* used to determine clinical significance on the Lab Results page. The Clinically Significant radio button on that page is available only if a variable that flags clinical significance has been defined for the study.

Analyte	Clinical Significance Criterion
Alkaline Phosphatase(ALP)	>= 3 x Upper Limit of Normal (ULN)
Alanine Aminotransferase (ALT)	>= 3 x ULN
Aspartate Aminotransferase (AST)	>= 3 x ULN
Bilirubin (BILI)	>= 2.0 mg/dL
Blood Urea Nitrogen (BUN)	>= 30 mg/dL
Creatine Kinase (CK)	>= 3 x ULN
Creatinine(CREAT)	>= 2.0 mg/dL
Eosinophils/Leukocytes (EOSLE)	>= 10%
Hematocrit (HCT)	Female: <= 32% AND >= 3% decrease from baseline Male: <= 37% AND >= 3% decrease from baseline
Hemoglobin (HGB)	Female: <= 9.5 g/dL Male: <= 11.5 g/dL
Lactic Dehydrogenase (LDH)	>= 3 x ULN
Neutrophils/Leukocytes (NEUTLE)	<= 15%
Platelet (PLAT)	Low: <= 75,000/mm^3 High: >= 700,000/mm^3
Uric acid	Female: >= 8.5 mg/dL Male: >= 10.5 mg/dL
Leukocytes (WBC)	Low: <= 2.8 THOU/uL High: >= 16 THOU/uL

7.3 Clinically Significant Vital Sign Values

The following criteria are used to determine if a vital sign measurement is clinically significant in a Clinically Significant Vitals Analysis, if you choose to use "built-in" criteria. The other option is to use a variable that flags clinical significance, if one has been defined for the study.

Measurement	Age	Clinical Significance Criterion
Weight (WEIGHT)	Any	Increase of >= 7% from baseline
Temperature (TEMP)	Any	Increase of >= 1.1°C to >= 38.3 °C
Heart rate (HR)	5 to 14 years	<= 50 bpm >= 140 bpm
	15 to 18 years	<= 50 bpm >= 120 bpm
	18 and above	<= 50 bpm >= 110 bpm
	Any	Decrease of >= 15 bpm from baseline Increase of >= 15 bpm from baseline
Systolic blood pressure (SYSBP)	7 to 12 years	<= 117mmHg >= 130 mmHg
	13 to 17 years	<= 120 mmHg >= 144 mmHg
	18 and above	<= 90 mmHg >= 150 mmHg
	Any	Decrease of >= 20 mmHg from baseline Increase of >= 20 mmHg from baseline
Diastolic blood pressure (DIABP)	7 to 12 years	<= 75 mmHg >= 86 mmHg
	13 to 17 years	<= 80 mmHg >= 92 mmHg
	18 and above	<= 50 mmHg >= 100 mmHg
	Any	Decrease of >= 15 mmHg from baseline Increase of >= 15 mmHg from baseline

