An Evaluation of the Readability of Drug Trials Snapshots

by

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Abstract

Health outcomes primarily depend on the health literacy of patients. It is important to assess the readability of patient health related materials like prescription information. The objective of this review was to evaluate readability of FDA approved Drug Trials Snapshots in order to determine if they are likely to be useful to consumers and patient advocacy groups. The reading ease and average grade level was measured of 59 currently FDA approved Drug Trials Snapshots and their corresponding Prescription labeling and Medication guides to evaluate the overall readability. The Flesch-Kinkaid Reading Ease test showed that the Snapshots had a higher reading ease than the Prescription labeling ($p<0.01$), but a lower reading ease than the Medication guides ($p<0.01$). In terms of the mean average grade level, the Snapshots had a lower grade level than the Prescription labeling ($p<0.01$) and a higher grade level than the Medication guides ($p<0.01$). The average grade level of the Snapshots was the 10^{th} grade which does not meet the recommended 6^{th} – 8^{th} grade level. The Drug Trial Snapshots are improvement readability wise in comparison to the Prescription labeling but are not better than the Medication guides. Hence, the Drug Trials Snapshots content may be useful for patients, but it may not be comprehensible for limited literacy patients.

Table of Contents

List of Tables

List of Figures

Introduction

Health literacy is an important component of patient health outcomes and management due to the importance of patients' understanding of the health care that they are receiving from healthcare professionals. According to Badarudeen and Sabharwal in 2010, health literacy is defined as the "capacity to obtain, interpret, and understand basic health information and services and the competence to use such information and services to enhance health" (Badarudeen & Sabharwal, 2010). According to Wilson (2009), about 47% of American adults have trouble understanding the complex health information given to them by their healthcare providers (Wilson, 2009). Therefore, approximately half of the population has varying degrees of health literacy.

Health literacy is dependent on various factors including the ability of health care professionals to communicate to the patient, the information accessible to the patient and the health awareness of the patient. The patient and their caregivers must be able to read and understand material provided to them in order to obtain or maintain a higher level of health care and treatment options. Due to the varying level of patient education and literacy levels, it is important that all forms of health information can be understood by all patients. Health literacy has many positive effects on the patient's care. For example, if patients are able to understand the care that they are given, then they would be able to better prepare themselves for their treatment plans and have better overall recovery (Cotugna, Vickery & Carpenter-Haefele, 2005).

Due to the importance of establishing health literacy in patient populations, there has been significant research regarding the various aspects of literacy. In a study conducted by Charbonneau in 2013, an assessment was done on the written literature prescription information

given to women undergoing hormone therapy for the treatment of their menopausal symptoms. The study concluded that the majority of prescription labeling reading literature had a significantly high grade level of 9.33. It also concluded that the health literacy of the women was lower than necessary and negatively affecting the health outcome of the patients (Charbonneau, 2013).

According to a study reviewing FDA approved medication guides study conducted by Wolf et al., (2006); medication guides were not useful to patients with limited literacy. In the study, the recommended reading difficulty level for healthcare materials was determined to be 6th to 8th grade on the Keystone Dialogue scale based on the education and literacy level of patient populations. It was also determined that none of the 40 medication guides reviewed met the reading difficulty level. In addition, the study concluded that medication guide materials accompanying potential harmful prescription medication are not useful to patients because the patients were unable to understand them (Wolf, Davis, Shrank, Neuberger, & Parker, 2006). While various studies have been conducted to determine the reading levels of traditional healthcare materials, there have not been studies conducted on some of the newer literature released to rectify the higher reading level of traditional healthcare materials.

Drug Trials Snapshots are new FDA published medical literature, which are available for consumers to use. They are used by patients especially when discussing a drug's risks and benefits with their physicians. The Drug Trials Snapshots initiative was started to meet the Section 907 of the Food and Drug Administration Safety and Innovation Act (FDASIA) requirement. The Section 907 recommends that the FDA should improve the quality and completeness of demographic subgroup data, identify the barriers to subgroup enrollment in clinical trials and increase the availability of this data to public. This initiative provides a

summary of drug information including the clinical trials information on the FDA website: FDA.gov. According to the FDA, the goal of the Drug Trials Snapshot was to create an alternative form of information about drugs that is easier to access and simple to understand by patients in a consumer-friendly language. This information could be used by the patient to educate themselves about their treatment options as well as to get more information about the demographics of the clinical trials. The Drug Trials Snapshots, as the name suggests, provides a basic summary of the drug, drug clinical trials information, and other pertinent information in a question and answer format. It provides information about sex, age, race, and ethnicity of participants of clinical trials. In addition, it includes the blue prints of the clinical trials, results of efficacy and safety studies within the demographic subgroups. The clinical trial data are represented in tabular format and easy to understand pictorial charts. A sample of Drug Trials Snapshot (Addyi) information is included in Appendix B. The Drug Trial Snapshot for Addyi includes basic information such as the purpose, usage, and benefits. It also summarizes the efficacy and possible effects of subgroups (sex, race, and age). Pictorial representation of participation, demographics and design of the clinical trials conducted are also published in the Snapshots. Drug Trials Snapshot information is published on the FDA website 30 days after the drug is approved. According to the FDA, the Drug Trials Snapshot is an improvement on traditional healthcare material like prescription information in the modern age of technology ("Drug Trials Snapshots," 2016).

To evaluate the effect on health literacy of the Snapshots, the reading ease (determined through the Flesch-Kinkaid reading ease scale of 1-100) and grade level (measured on a scale from 1-12) of the Snapshots need to be assessed. These two aspects will provide an overall

understanding of the readability of the text. There are various tests available in order to assess the reading ease and grade level of any given text.

According to Badarudeen and Sabharwal (2010), the Flesch Kincaid Grade, the Gunning Fog Index, and the SMOG readability formula are all various tests used to determine the grade level of a given text. Specifically, the SMOG Readability formula is recommended by the National Cancer Institute for cancer pamphlets. Each of the grade level tests, Flesch Kincaid, Gunning-Fog, Cloeman-Liau Index, SMOG Index, and Readability Index are calculated using different formulae. The average of these test scores would give an accurate grade level. All of these tests are available for low costs on various website services including Microsoft Word and paid services (Badarudeen & Sabharwal, 2010). Based on the studies that assessed the readability of similar literature and convenience, Flesch-Kinkaid reading ease scale and Average grade level was used to determine the readability of Drug Trials Snapshots.

In the previously mentioned study regarding material given to women undergoing hormonal therapy, Charbonneau (2013) used the Flesch Reading Ease since it is one of the most common readability measurement tools. The Flesch Reading Ease analyzes the ease of reading on a scale from 0 to 100 (0 being difficult to read and 100 being easy to read). It provides a quantitative measurement of the reader's ability to read the particular document. This scale is also used by the government to assess readability. For example, the Florida state government requires that life insurance policies to have a Flesch Reading Ease score no less than 45 (Charbonneau, 2013).

The purpose of this review is to evaluate the Drug Trials Snapshots in terms of its reading ease and grade level to determine if the Snapshot initiative is an improvement upon the traditional medical literature present. Hence, the Drug Trials Snapshots was compared to

Prescription labeling and Medication guides, both comparable and widely used material for providing drug information to patients. The review is sought to address two key questions: (1) what is the readability of the Drug Trials Snapshots published on the FDA website? and (2) How does the readability of the Drug Trials Snapshots compare to that of the Prescription labeling and Medication guides? The answers to these questions will help us assess whether the information in the Snapshots satisfies the FDA's goal of providing transparency and useful information regarding the newly approved drugs to patients **(**Wolf et al., 2006).

Methods

To compare the reading ease and grade level of the Drug Trials Snapshots, Medication guides and Prescription labeling, the text of these were obtained for the 59 drugs published before May 2016 on the FDA website ("Drug Trials Snapshots," 2016). The text was then analyzed and tested using a paid service readability tool on the website, Readability-score.com ("Readability-score.com," 2016). This website was selected since it included the tests suggested by Badarudeen & Sabharwal (2010) and was convenient to use without any size limit for the text. The text from the FDA Snapshot, Prescription labeling, and Medication guides were copied and placed into a text box on this website, which then used mathematical algorithms to calculate both the reading ease and the grade level of the particular test. This website used the Flesch-Kinkaid Reading Ease readability test to analyze the text for reading ease. It also used the following grade level tests to determine the grade level of the text: Flesch-Kincaid Grade Level, Gunning-Fog Score, Cloeman-Liau Index, SMOG Index, and Automated Readability Index. Since various tests were used to evaluate the grade level, the website used also provided an average grade level. This was used in the analysis of the grade level rather than each individual test to have a more holistic evaluation. The Flesch-Kinkaid Reading Ease, and the grade level of

the text Flesch-Kincaid Grade Level, Gunning-Fog Score, Cloeman-Liau Index, SMOG Index, and Automated Readability Index are tabulated in Appendix A.

Once the reading ease score and the average grade level were obtained, two two-sample t-Tests were conducted to examine any of the differences between the mean reading ease score of the Snapshots and that of the Prescription labeling, as well as any of the differences between the mean reading ease score of the Snapshots and that of the Medication guides. A second set of two two-sample t-Tests were done to determine any of the differences between the mean average grade level of the Snapshots and that of the Prescription labeling as well as any of the differences between the mean average grade level of the Snapshots and that of the Medication guides.

Results

To evaluate and compare the readability of the Drug Trials Snapshots, with that of the Prescription labeling and Medication guides, two variables were analyzed: reading ease and average grade level. In terms of the reading ease (calculated through the Flesch-Kinkaid Reading Ease test), the 59 Snapshots had a mean reading ease score of 55.77, while the corresponding 59 Prescription labeling had a mean reading ease score of 50.18 and the corresponding 41 Medication guides had a mean reading ease score of 65.29 shown in Figure 1. There were only 41 Medication guides due to the fact that they were not available for all of the drugs which had Snapshots available. Based on these results, the Snapshots had a higher reading ease score than the Prescription labeling, however, had a lower reading ease score than the Medication guides.

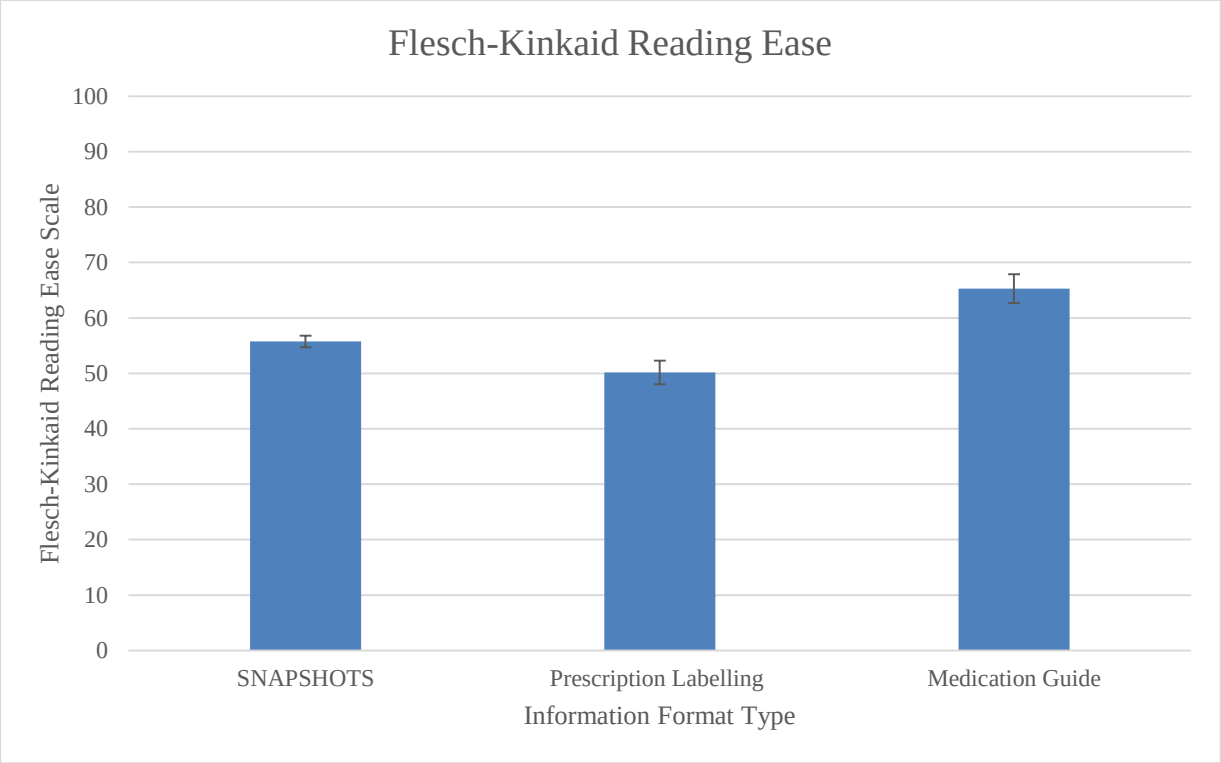

Figure 1: Comparison of the Reading Ease of 59 Snapshots and their corresponding 59 Prescription labeling & 41 Medication Guides. The error bars represent a 95% Confidence Interval.

The second variable analyzed was the grade level. This was calculated by averaging the results of the Flesch-Kincaid Grade Level, Gunning-Fog Score, Cloeman-Liau Index, SMOG Index, and Automated Readability Index tests. The Snapshots had a mean Average grade level of 10.1 while the Prescription labeling and Medication guides had mean Average grade levels of 10.78 and 8.83 respectively, shown in Figure 2. Hence, the Snapshots had a lower mean Average grade level value than the Prescription labeling, but a higher mean Average grade level value than the Medication guides.

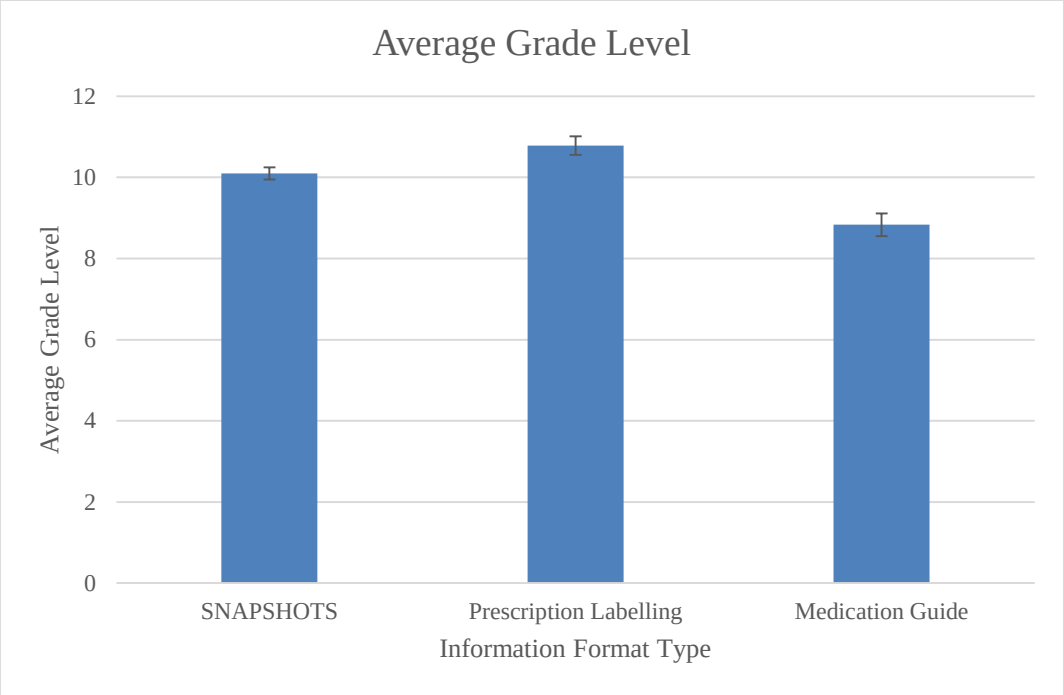

Figure 2: Comparison of the Average Grade Level of 59 Snapshots and their corresponding 59 Prescription labeling & 41 Medication guides. The error bars represent a 95% Confidence Interval.

To further analyze the differences in the means of the two variables: reading ease and average grade level, two t-Test statistical tests were done between the means of the Snapshots and Prescription labeling (one for reading ease and one for average grade level), and two t-Test statistical tests (one for reading ease and one for average grade level) were done between the means of the Snapshots and the Medication guides. The results of the tests are shown in Tables 1 and 2. Since the p-values of all of the tests are lower than the 0.05 alpha level ($p < 0.01$), the differences between the means of the reading ease and the grade level are determined to be statistically significant, rejecting the null hypothesis that the differences between the means were due to random chance. This shows that there is a statistically significant improvement in the readability of the Snapshots in comparison to the previously used Prescription labeling measured

through the reading ease and the grade level, and that the Snapshots did not have a statistically significant improvement in readability in comparison to the Medication guides.

t-Test: Two-Sample Assuming Unequal Variances			
Reading Ease			
	Snapshots	Prescription Labeling	Medication Guide
Mean	55.77	50.18	65.29
Variance	16.27	66.54	30.49
Observations	59	59	41
Hypothesized Mean Difference		0	0
df		58	40
Standard Deviation	4.03	8.16	8.22
Standard Error	0.525	1.061	1.284
95% Confidence Interval	1.051	2.125	2.579
P value		9.25×10^{-6}	4.89×10^{-14}

Table 1: Results of the t-Test used to compare the means of the Reading ease of the Snapshots, the Prescription labeling and the Medication guides

t-Test: Two-Sample Assuming Unequal Variances			
Average Grade Level			
	Snapshots	Prescription Labeling	Medication Guide
Mean	10.1	10.78	8.83
Variance	0.32	0.78	0.40
Observations	59	59	41
Hypothesized Mean Difference		0	0
df		58	40
Standard Deviation	0.57	0.88	0.89
Standard Error	0.074	0.115	0.139
95% Confidence Interval	0.148	0.230	0.280
P value		2.66×10^{-6}	3.09×10^{-16}

Table 2: Results of the t-Test used to compare the means of the Average grade level of the Snapshots, the Prescription Labeling, and the Medication guides

Discussion

The Reading ease and the Average grade level of the Drug Trials Snapshots were statistically different from that of the corresponding Prescription labeling and Medication guides. In regards to the Reading ease, the Snapshot had a statistically significant higher reading ease score than that of the Prescription labeling, indicating that it is easier to read. However, Snapshots also had a statistically significant lower reading ease score than that of the Medication guides, indication that it is harder to read. In terms of the grade level, the Snapshots had a statistically significant lower average grade level than that of the Prescription labeling. On the other hand, the average grade level of the Snapshots was statistically significantly higher than that of the Medication guides.

The results of this review suggest that there has been a slight improvement in the readability of the material provided to patients and caregivers through Snapshots about their healthcare and drug information in comparison to the Prescription labeling. However, the mean of the average grade level of Snapshots was still significantly higher than the suggested grade level of 6th to 8th grade. In terms of the reading ease, if the Florida State laws are used as an example, the reading ease scores of the Snapshots, Prescription labeling and Medication guides are well above the required score of 45 or above. Also, according to Wilson's (2009) interpretation of the Flesch Reading Ease score, a score from 40-59 is fairly difficult and is estimated to have a reading grade between 10th and 11th grade (Wilson, 2009). Since the Drug Trial Snapshots reading ease is above 55 and Average grade level is above 10th grade, it is difficult for the patient to comprehend. Hence, the interpretation of the data indicates that there is room for improvement of Drug Trial Snapshots readability. The Snapshots falls short of

improving health literacy since it is still incomprehensible for the patient populations of lower literacy levels.

To further analyze the readability of the Drug Trial Snapshots, the drugs were categorized according to their indication. Three major groups (indications that had three or more drugs) emerged: cancer drugs, cardiovascular drugs, and antipsychotic drugs. For the cancer drugs, the average Flesch-Kinkaid reading ease and grade levels were 54.68 and 10.21 respectively. The cardiovascular drugs' average Flesch-Kinkaid reading ease and grade levels were 57.77 and 9.60 respectively. The antipsychotic drugs had an average Flesch-Kinkaid reading ease and grade levels of 56.47 and 9.83 respectively. Overall, the cardiovascular drugs had a higher reading ease and a lower grade level than the cancer and antipsychotic drugs. This could be due to the widespread use of these drugs and the fact that it is easier to understand heart related diseases than cancer and psychosis (since cardiac failure is well researched and known by the public). Along the same trend, the cancer drugs had the lowest reading ease and highest grade level than the cardiovascular and antipsychotic drugs. This could be due to the complexity of cancer and its treatment. In addition, cancer is still being researched and new information is still emerging.

Through this review, it is determined that the Snapshots are an improvement upon the Prescription labeling; however, they are still harder to read than the Medication guides. Upon further review, there is evidence that there is a need for more improvement in order to completely resolve the concerns brought up by the Keystone Dialogue. In addition, when grouped by indication, a trend of lower reading ease and higher grade level was seen among cancer drugs. It is suggested that the Snapshots are further reviewed and the reading ease of the text is increased while reducing the grade level of the text. This will be a vital step in order to improve the overall health literacy of patient populations

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APPENDIX A

	Drug TrialsSnapshot							Prescription Labeling							Medication Guides						
Drug Name/ Formula	Flesch-Kinkaid**ReadingEase**	Flesch-KincaidGradeLevel	Gunning-Fog Score	Cloeman-Liau Index	SMOG Index	AutomatedReadability Index	**Average GradeLevel**	Flesch-Kinkaid**ReadingEase**	Flesch-KincaidGradeLevel	Gunning-Fog Score	Cloeman-Liau Index	SMOG Index	AutomatedReadability Index	**Average GradeLevel**	Flesch-Kinkaid**ReadingEase**	Flesch-KincaidGradeLevel	Gunning-Fog Score	Cloeman-Liau Index	SMOG Index	AutomatedReadability Index	**Average GradeLevel**
Addyi	59.8	7.5	9.9	13.1	10.3	6.9	9.5	47.9	8.2	10.5	18.2	9.7	9	11.1	69.5	5.8	8.8	12.8	9.4	6	8.6
Alecensa	58.9	7.6	9.8	13.5	10.2	7.1	9.6	58.1	6.9	10.3	16.7	9.8	8.1	10.4	63.1	6.5	8.2	14.2	9	6.7	8.9
Anthim	52.4	8.5	11.1	14.6	11	8.1	10.7	50.8	7.7	9.8	17.7	9.4	8.6	10.6	61.1	6.5	9.3	14.7	9.4	6.5	9.3
Aristada	55.4	7.9	10	13.6	10.2	6.9	9.7	50.7	7.5	9.6	18.6	8.9	8.8	10.7	60.9	6.9	9.4	14.1	9.7	6.9	9.4
Avycaz	52.9	8.6	11.1	13.9	11	7.8	10.5	38.4	9.7	12.7	18.7	10.8	9.8	12.3	-	-	-	-	-	-	-
Bridion	51.9	8.7	10.8	14.6	10.8	8.3	10.6	37	9.7	11.1	19	9.9	9.7	11.9	-	-	-	-	-	-	-
Briviact	57.5	7.8	10.2	13.9	10.4	7.4	9.9	44.1	8.7	11.2	19	10	9.6	11.7	58.3	7.2	9.9	15.3	9.9	7.6	10
Cholbam	63.3	7	9.1	13.9	9.8	7.5	9.5	56.4	7.3	10.6	16.4	10.1	8.3	10.5	-	-	-	-	-	-	-
Cinquair	58.1	7.6	9.6	14.3	10	7.5	9.8	50.4	7.9	11.2	16.9	10.1	8.1	10.8	-	-	-	-	-	-	-
Corlanor	57.7	7.9	9.4	13.7	10	7.5	9.7	46.2	8.4	11.4	18	10	8.7	11.3	-	-	-	-	-	-	-
Cosentyx	55.4	8.3	10.5	14.3	10.7	8.3	10.4	59.7	6.7	9.5	14.8	9.5	6.7	9.4	65.2	6.3	8.8	13.3	9.4	6.1	8.8
Cotellic	51.3	9.1	11.3	14.3	11.3	8.8	11	55.2	7.1	9.4	19.3	9.1	9.7	10.9	68.9	5.7	8.1	13.4	8.9	6	8.4
Cresemba	55.4	8.1	10.6	14.3	10.7	7.9	10.3	37.1	9.7	11.9	18.8	10.3	9.5	12	60.6	6.5	9.3	14.9	9.3	6.5	9.3
Daklinza	59.4	7.3	9.6	13.5	10	6.8	9.4	47.5	8.1	11.5	17.7	9.9	8.3	11.1	62.6	6.2	9.1	14.2	9.2	5.9	8.9
Dalvance	52	8.9	10.8	14.4	10.9	8.5	10.7	47.5	8.2	11.3	18	10	8.8	11.3	-	-	-	-	-	-	-
Darzalex	56.7	7.8	9.8	13.4	10.2	6.9	9.6	48.7	8	11.6	17.7	10	8.4	11.1	60	6.7	9.6	13.9	9.5	6	9.1
Defitelio	55	8.2	10.1	14.3	10.3	7.8	10.1	40	9.4	12.2	18.1	10.6	9.2	11.9	-	-	-	-	-	-	-
Empliciti	48.5	9.3	11.2	14.3	11.1	8.3	10.8	51.6	7.4	9.7	18.3	9	8.5	10.6	55	7.4	9.9	15.9	9.7	7.6	10.1
Entresto	59.1	7.6	9	13.7	9.7	7.3	9.5	54	7.1	8.4	18.5	8.5	8.8	10.3	62.5	6.7	9	13.4	9.5	6.3	9
Entyvio	48.5	9.4	12.1	14.7	11.7	8.8	11.3	40.7	9	11.3	18.1	9.8	8.6	11.4	57.8	7	8.7	13.9	9.2	6.1	9
Farydak	54.5	8.1	10.4	14.6	10.5	7.9	10.3	45	8.3	10	19.4	9.1	9.4	11.2	71.9	5	7.4	12.7	8.4	4.8	7.7
Genvoya	55.9	8.1	10.4	13.4	10.6	7.3	10	39	9.3	11.8	18.2	9.9	8.7	11.6	67.2	5.7	8.6	14	9.1	6.1	8.7
Ibrance	50.9	9.2	11.7	14.5	11.5	8.9	11.2	47.6	7.9	9.3	19.4	8.7	9.3	10.9	75	4.4	7.8	14.2	8.5	5.9	8.2
Jublia	57.8	7.8	9.2	13.8	9.8	7.5	9.6	55	7	9.7	16.2	9.2	7.1	9.8	59.4	6.8	8.6	13.6	9.1	5.7	8.8
Kanuma	61.1	7.5	9.7	13.3	10.1	7.4	9.6	51.6	7.6	10.2	17.2	9.5	8.1	10.5	-	-	-	-	-	-	-
Kengreal	55.7	8.4	10.6	13.3	10.8	7.7	10.2	45.5	8.2	9.2	17.7	8.7	7.9	10.3	-	-	-	-	-	-	-
Kybella	60.4	7.2	9.7	13.4	10	6.8	9.4	48.9	7.9	10.3	17.3	9.5	8	10.6	60	7.1	10.1	14.5	10.1	7.2	9.8
Lenvima	53.1	8.3	10.6	14.7	10.6	7.9	10.4	36.4	9.9	9.3	22	9.4	12.3	12.6	71.6	4.9	7.5	14.5	8.4	6.2	8.3
Lonsurf	58.4	7.7	10.3	14	10.5	7.7	10	57.5	6.6	8.4	17.8	8.5	8.1	9.9	69.3	5.6	8.2	14.1	8.9	6.4	8.6
Natpara	45.5	9.8	11.7	14.8	11.4	8.9	11.3	48.4	8.2	11.1	17.1	10.1	8.4	11	67.1	5.9	8.1	12.5	8.9	5.2	8.1
Ninlaro	55.9	7.9	10.4	14.3	10.5	7.5	10.1	52.9	7.3	11	17.5	9.7	8.2	10.7	65.6	6	8	13.6	8.8	6	8.5
Odomzo	55.7	7.7	9.6	13.8	9.9	6.7	9.5	49.2	8.3	10.8	16.6	10.3	8.4	10.9	67.5	6	8.4	13.1	9.2	6.1	8.6
Orkambi	56.5	7.9	9.5	13.4	10	7	9.6	58.3	6.6	10.7	16.7	9.6	7.6	10.2	68	5.7	8.4	13.5	9	5.9	8.5
Portrazza	58.6	7.7	10.3	13.7	10.5	7.4	9.9	46.2	8.6	11.3	18.3	10.3	9.4	11.6	-	-	-	-	-	-	-
Praluent	56.4	7.6	10.3	13.5	10.3	6.5	9.6	44.3	8.4	10.2	19.1	9.2	9.2	11.2	62.4	6.8	9.3	13.8	9.8	6.7	9.3
Praxbind	56.5	7.8	10	14.2	10.3	7.5	10	40.4	9.4	11.7	19.4	10.5	10.4	12.3	-	-	-	-	-	-	-
Repatha	45.1	10.1	11.8	14.6	11.6	9.2	11.5	61.4	6.4	9.7	14.8	9.5	6.5	9.4	58.9	7.4	9.9	14.1	10.2	7.3	9.8
Rexulti	54.2	8.2	10.5	14	10.6	7.6	10.2	55.2	6.8	10.4	18	9.1	8.2	10.5	62.2	6.7	9.7	14.2	9.9	6.9	9.5
Ryzodeg	65.8	6.9	9.3	13	9.9	7.3	9.3	67.4	5.3	9.4	16.2	9.1	7.1	9.4	79.6	4.3	8.2	12.9	9	5.9	8.1
Savaysa	55.5	8.4	10.4	13.3	10.6	7.5	10	62.4	6.2	8.8	15.3	9	6.7	9.2	71.3	5.1	7.7	12.2	8.6	4.7	7.7
Sivextro	52.4	8.9	11.2	14.2	11.2	8.6	10.8	38.5	9.3	9.9	18.6	9.2	9	11.2	-	-	-	-	-	-	-
Stiolto Respimat	55.6	8.2	9.7	13.7	10.2	7.6	9.9	33.3	10.8	13	18.4	11.5	10.3	12.8	57.9	7.3	9.4	14.5	9.7	7	9.6
Strensiq	54.9	8.4	11.3	14.7	11.2	8.6	10.8	69.1	5.2	9.1	15.3	9	6.6	9	63.3	6.3	9.7	14.7	9.7	6.8	9.4
Tagrisso	53.3	8.9	11	13.8	11.1	8.4	10.6	49.1	7.8	9.8	18.8	9.1	9.1	10.9	69.4	5.5	7.7	13.2	8.7	5.7	8.2
Taltz	57.8	7.7	10.7	14.3	10.6	7.6	10.2	47.9	8.1	9.7	18.3	9.2	8.9	10.8	72.1	5.4	8.7	12.1	9.4	5.3	8.2
Tresiba	65.8	6.7	9.2	13	9.8	6.9	9.1	61.5	6.1	9.7	17	9.1	7.6	9.9	68.4	6	9.2	12.9	9.7	6.2	8.8
Unituxin	61	7.3	9.7	14	10.1	7.6	9.7	44.3	8.6	11.5	18.6	10	9.2	11.6	-	-	-	-	-	-	-
Uptravi	56.5	7.8	10.3	13.6	10.4	6.9	9.8	47.9	8.2	11.5	16.7	10.2	7.9	10.9	-	-	-	-	-	-	-
Varubi	57.7	7.7	9.8	12.9	10.2	6.6	9.4	45.5	8.5	11.6	17.1	10.1	8.1	11.1	56.9	7.5	10	14.1	10.1	6.9	9.7
Veltassa	56	7.9	10.7	13.8	10.6	7.2	10	56.6	7	9.7	15.6	9.5	7	9.8	67.9	5.9	8	12.1	8.9	5.2	8
Venclexta	52	8.8	10.6	14.3	10.8	8.4	10.6	55.3	6.9	7.9	17.4	8.3	7.8	9.7	72.7	5	7.1	13	8.2	5.3	7.7
Viberzi	56.2	8.1	10.2	13.5	10.5	7.5	10	48.6	8.2	11.6	17.1	10.3	8.4	11.1	66.2	6.2	8.6	12.9	9.3	5.8	8.6
Vistogard	57.6	7.8	10.1	14.2	10.3	7.7	10	55.3	7.2	10.7	16.2	9.9	7.6	10.3	68.8	5.8	8.4	14.7	9.2	7.3	9.1
Vraylar	59.8	7.4	10	13.4	10.3	7	9.6	43.5	9	10.1	19.4	9.8	10.4	11.7	-	-	-	-	-	-	-
Xuriden	56.7	7.8	10.2	13.3	10.4	6.9	9.7	65.7	5.6	9.2	14.5	9.1	5.9	8.9	-	-	-	-	-	-	-
Yondelis	52.3	8.5	11	15.1	10.9	8.5	10.8	49.6	7.9	9.8	19	9.3	9.5	11.1	68.5	5.7	8.3	14.4	9	6.7	8.8
Zepatier	55.9	7.9	9.8	13.7	10.1	7.1	9.7	62.3	5.7	10.2	16.8	8.9	7	9.7	-	-	-	-	-	-	-
Zontivity	51.3	9.3	11	14.1	11.1	9	10.9	59.9	6	9.5	17.3	8.6	7.4	9.8	-	-	-	-	-	-	-
Zurampic	54.7	8.1	9.9	14.2	10.2	7.6	10	51.9	7.9	11	16.4	10.3	8.1	10.7	62.3	6.6	8.7	14.3	9.3	6.8	9.1

APPENDIX B

ADDYI (flibanserin)
(add-ee)
Sprout Pharmaceuticals, Inc.
Approval date: August 18, 2015

DRUG TRIALS SNAPSHOT SUMMARY:

What is the drug for?

ADDYI is a drug for the treatment of acquired, generalized hypoactive sexual desire disorder (HSDD) in women who have not gone through menopause.

Women with HSDD have low sexual desire that is troubling to them. Their low sexual desire is **not** due to:

- a medical or mental health problem
- problems in the relationship
- a medicine or other drug use

HSDD is acquired and generalized if the woman has not had problems with low sexual desire in the past, and if she has symptoms no matter the type of sexual activity, the situation, or the sexual partner.

How is this drug used?

ADDYI is a tablet that is taken once daily at bedtime.

What are the benefits of this drug?

In clinical trials, ADDYI increased the number of satisfying sexual events, improved sexual desire and reduced distress related to low sexual desire. On average, the improvements are small but some women find the improvements to be meaningful.
MORE INFO

What are the benefits of this drug (results of trials used to assess efficacy)?

The efficacy of ADDYI was studied in three double-blind, placebo-controlled trials. The efficacy results are based on the full analysis set comprised of all randomized patients who took at least one dose of study medication and had at least one on-treatment efficacy assessment. Missing values were imputed using last-observation-carried-forward. The unadjusted means are presented for the baseline values.

The table below summarizes the results for the two co-primary efficacy endpoints (satisfying sexual events and sexual desire) and a secondary endpoint (distress related to having low sexual desire) at week 24.

Table 2. Efficacy Results in Premenopausal HSDD Patients by Trial

	Trial 1		Trial 2 [1]		Trial 3	
	ADDYI	Placebo	ADDYI	Placebo	ADDYI	Placebo
Full Analysis Set	n=280	n=290	n=365	n=372	n=532	n=536
Number of satisfying sexual events (per 28 days)						
Baseline (Mean)	3.0	2.7	2.6	2.7	2.5	2.7
Change from baseline (Mean)	1.6	0.8	1.8	1.1	2.5	1.5
Treatment diff.	0.9		0.6		1.0	
(95% CI)	(0.3,1.4)		(-0.03, 1.2)		(0.4, 1.5)	
Change from baseline (Median)	1.0	0.0	1.0	0.5	1.0	0.5
Median treatment difference	1.0		0.5		0.5	
p-value vs placebo	*p<0.01*		*p<0.01*		*p<0.0001*	
e-Diary Desire						
Baseline (Mean)	12.9	11.8	12.1	10.2	*Not Used*	*Not Used*
Change from baseline at Week 24 (Mean)	9.1	6.9	8.3	6.7		
Treatment diff.	2.3		1.7			
(95% CI)	(-0.1, 4.7)		(-0.5, 4.0)			
p-value vs placebo	NS		NS			
FSFI Desire						
Baseline (Mean)	1.9	1.9	1.8	1.8	1.9	1.9
Change from baseline at Week 24 (Mean)	0.9	0.5	0.9	0.5	1.0	0.7
Treatment diff.	0.4		0.3		0.3	
(95% CI)	(0.2, 0.5)		(0.2, 0.5)		(0.2, 0.4)	
p-value vs placebo	*N/A* [2]		*N/A* [2]		*p<0.0001*	
FSDS-R Question 13 [3]						
Baseline (Mean)	3.2	3.2	3.2	3.2	3.4	3.4
Change from baseline at Week 24 (Mean)	-0.8	-0.5	-0.8	-0.5	-1.0	-0.7
Treatment diff.	-0.4		-0.3		-0.3	
(95% CI)	(-0.5, -0.2)		(-0.4, -0.1)		(-0.4, -0.1)	
p-value vs placebo	N/A [2]		N/A [2]		*p=0.0001*	

CI = Confidence Interval; NS= not statistically significant; *N/A*=not applicable
Shaded cells show the results for the co-primary efficacy endpoints for each trial.
e-Diary desire was evaluated as a co-primary endpoint in Trials 1 and 2. FSFI desire was evaluated as a co-primary endpoint in Trial 3 and as a secondary endpoint in Trials 1 and 2.
For satisfying sexual events, p-values are based on the Wilcoxon rank sum test stratified by pooled center. Median change from baseline is shown because the data are not normally distributed.
For FSFI-desire, e-Diary desire, and FSDS-R Question 13, reported p-values are based on an ANCOVA model using baseline as a covariate with treatment and pooled center as main effect terms. For the change from baseline, the adjusted least squares mean (standard error) are presented.
[1]Excludes subjects from two study sites that had data integrity issues
[2]p-value not reported for secondary endpoints because the trial failed on the eDiary Desire co-primary efficacy endpoint
[3]A decrease in score represents improvement

Source: ADDYI Prescribing Information, Section 14, Table 6

Were there any differences in how well the drug worked in clinical trials among sex, race and age?

Subgroup analysis was conducted for race.

Sex: All patients in the trials were women.

Race: The majority of patients in the trials were white. Differences in how well ADDYI worked among races could not be determined.

Age: All patients in the trials were women between 18 and 56 years of age. Differences in how well ADDYI worked in patients below and above 65 years of age could not be determined.

MORE INFO

Were there any differences in how well the drug worked in clinical trials among sex, race, and age groups?

Tables 3, 4, and 5 below summarize the efficacy results by race for the three important outcome measures in clinical trials.

Table 3. Subgroup Analysis by Race: Change From Baseline in Monthly Number of Satisfying Sexual Events (SSEs)*

Subgroup	Trial 1 (N=570)			Trial 2 (N=737)			Trial 3 (N=1068)		
	ADDYI vs. Placebo**	95% CI		ADDYI vs. Placebo**	95% CI		ADDYI vs. Placebo**	95% CI	
		LL	UL		LL	UL		LL	UL
Race									
White	0.9	0.3	1.4	0.5	-0.07	1.1	0.9	0.4	1.5
Black or African American	-0.1	-2.7	2.5	1.2	-3.0	5.4	0.7	-1.3	2.7
Asian	7.6	-1.1	16.4	0.3	-4.4	5.0	5.3	1.4	9.2
American Indian or Alaska Native	N/A	N/A	N/A	N/A	N/A	N/A	2.9	-4.0	9.8
Native Hawaiian or Other Pacific Islander	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

*Full Analysis Population Set
**Treatment difference between ADDYI and placebo was calculated by subtracting the monthly SSEs at baseline from the SSEs at the end of study (Difference >0 indicates treatment benefit of ADDYI compared to Placebo)
LL= lower limit; UL=upper limit; CI = confidence interval; N/A= Not applicable
Source: FDA analysis

Table 4. Subgroup Analysis by Race: Change From Baseline in the Desire Domain of Female Sexual Function Index (FSFI Desire)†*

Subgroup	Trial 1 (N=570)			Trial 2 (N=737)			Trial 3 (N=1068)		
	ADDYI vs. Placebo**	95% CI		ADDYI vs. Placebo	95% CI		ADDYI vs. Placebo	95% CI	
		LL	UL		LL	UL		LL	UL
Race									
White	0.3	0.1	0.5	0.4	0.2	0.5	0.4	0.2	0.5
Black or African American	0.6	-0.04	1.2	-0.2	-0.9	0.6	-0.3	-0.6	0.1
Asian	0.7	-0.5	1.9	0.01	-1.4	1.4	0.1	-2.4	2.5
American Indian or Alaska Native	N/A	N/A	N/A	N/A	N/A	N/A	1.6	0.5	2.7
Native Hawaiian or Other Pacific Islander	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

* Full Analysis Population Set
** Treatment difference between ADDYI and placebo was calculated by subtracting the monthly FSFI Desire score at baseline from the FSFI Desire score at the end of study (Difference >0 indicates treatment benefit of ADDYI compared to Placebo)
† FSFI desire was evaluated as a secondary endpoint in Trials 1 and 2 and as a co-primary endpoint in Trial 3. e-Diary desire was evaluated as a co-primary endpoint in Trials 1 and 2; Trials 1 and 2 failed on the e-Diary desire so subgroup results are not shown for this endpoint.
LL= lower limit; UL=upper limit; CI = confidence interval; N/A= Not applicable
Source: FDA analysis

Table 5. Subgroup Analysis by Race: Change From Baseline in Distress Measured by Question 13 of the Female Sexual Distress Scale-Revised (FSDS-R Q13)*

Subgroup	Trial 1 (N=570)			Trial 2 (N=737)			Trial 3 (N=1068)		
	ADDYI vs. Placebo**	95% CI		ADDYI vs. Placebo**	95% CI		ADDYI vs. Placebo**	95% CI	
		LL	UL		LL	UL		LL	UL
Race									
White	-0.3	-0.5	-0.1	-0.2	-0.4	-0.1	-0.3	-0.5	-0.2
Black or African American	-0.3	-1.0	0.3	0.2	-0.6	0.9	0.2	-0.3	0.6
Asian	-1.8	-3.0	-0.6	-0.7	-2.7	1.4	-0.6	-1.6	0.5
American Indian or Alaska Native	N/A	N/A	N/A	N/A	N/A	N/A	-1.0	-3.2	1.2
Native Hawaiian or Other Pacific Islander	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

* Full Analysis Population Set
** Treatment difference between ADDYI and placebo was calculated by subtracting the monthly FSDS-R Q13 score at baseline from the FSDS-R Q13 score at the end of study (Difference <0 indicates treatment benefit of ADDYI compared to Placebo)
LL= lower limit; UL=upper limit; CI = confidence interval; N/A= Not applicable
Source: FDA analysis

What are the possible side effects?

The most common side effects are dizziness, sleepiness, nausea, fatigue, insomnia, and dry mouth.

ADDYI may cause severe low blood pressure and fainting (loss of consciousness). Patients who use alcohol or who have liver problems must not take ADDYI because they will be at increased risk of severe low blood pressure and fainting (loss of consciousness). Taking ADDYI with certain medications also increases these risks. Patients should discuss all of their medications with their healthcare provider before being prescribed ADDYI. Patients should not start taking new medicines while taking ADDYI until checking it is safe to do so with their healthcare provider.

MORE INFO

What are the possible side effects (results of trials used to assess safety)?

The table below summarizes adverse reactions for the pooled four trials. The population represented is the Safety population, which includes any patient who received at least one dose of ADDYI or placebo drug.

Table 5. Adverse Reactions Reported in ≥2% of Patients Receiving ADDYI and at a Higher Incidence than Placebo-treated Patients

Adverse Reaction	Placebo (N=1556)	ADDYI (N=1543)
Dizziness	2.2%	11.4%
Somnolence	2.9%	11.2%
Nausea	3.9%	10.4%
Fatigue	5.5%	9.2%
Insomnia	2.8%	4.9%
Dry mouth	1%	2.4%

Source: ADDYI Prescribing Information, Section 6, Table 2

Were there any differences in side effects among sex, race and age?

Subgroup analysis was conducted for race.

Sex: All patients in the trials were women.

Race: The majority of patients in the trials were white. Differences in side effects among races could not be determined.

Age: All patients in the trials were women between 18 and 56 years of age. Differences in side effects in patients below and above 65 years of age could not be determined.

MORE INFO

Were there any differences in side effects of the clinical trials among sex, race, and age groups?

The tables below summarize dizziness, somnolence, and nausea by race. The population represented is the Safety population, which includes any patient who received at least one dose of ADDYI or placebo drug.

Table 6. Subgroup Analysis of Adverse Event-Dizziness

Subgroup	ADDYI (N=1543)		Placebo (N=1556)	
	n (%)	Total, n	n (%)	Total, n
White	163 (12.0)	1364	34 (2.5)	1379
Black or African American	6 (4.5)	134	0 (0.0)	122
Asian	3 (14.3)	21	0 (0.0)	21
American Indian or Alaska Native	1 (50.0)	2	0 (0.0)	7
Native Hawaiian or Other Pacific Islander	0 (0.0)	1	0 (0.0)	2
Unknown	3 (14.3)	21	0 (0.0)	25

Source: Company Trial Data

Table 7. Subgroup Analysis of Adverse Event-Somnolence

Subgroup	ADDYI (N=1543)		Placebo (N=1556)	
	n (%)	Total, n	n (%)	Total, n
White	148 (10.9)	1364	40 (2.9)	1379
Black or African American	23 (17.2)	134	2 (1.6)	122
Asian	2 (9.5)	21	1 (4.8)	21
American Indian or Alaska Native	0 (0.0)	2	1	7
Native Hawaiian or Other Pacific Islander	0 (0.0)	1	0	2
Missing	0 (0.0)	21	1 (4.0)	25

Source: Company Trial Data

Table 8. Subgroup Analysis of Adverse Event-Nausea

Subgroup	ADDYI (N=1543)		Placebo (N=1556)	
	n (%)	Total, n	n (%)	Total, n
White	142 (10.4)	1364	56 (4.1)	1379
Black or African American	8 (6.0)	134	4 (3.3)	122
Asian	6 (2.9)	21	0 (0.0)	21
American Indian or Alaska Native	1 (50.0)	2	0 (0.0)	7
Native Hawaiian or Other Pacific Islander	0 (0.0)	1	0 (0.0)	2
Unknown	4 (19.0)	21	0 (0.0)	25

Source: Company Trial Data

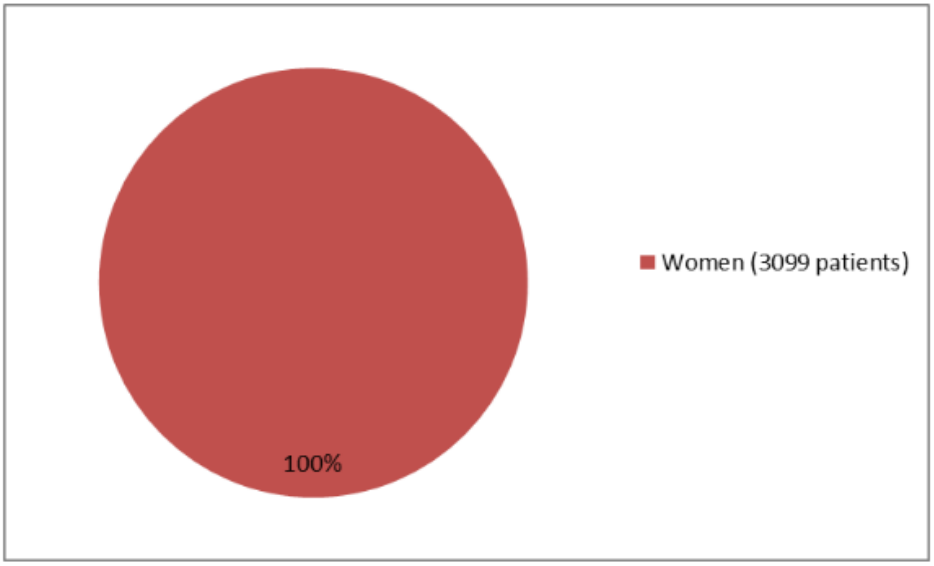
WHO WAS IN THE CLINICAL TRIALS?

Who participated in the clinical trials?

The FDA approved ADDYI based on evidence from 4 clinical trials of 3099 women with low sexual desire disorder. The trials were conducted in the United States, Canada, and Europe.

The figure below summarizes how many patients participated by sex in the clinical trials.

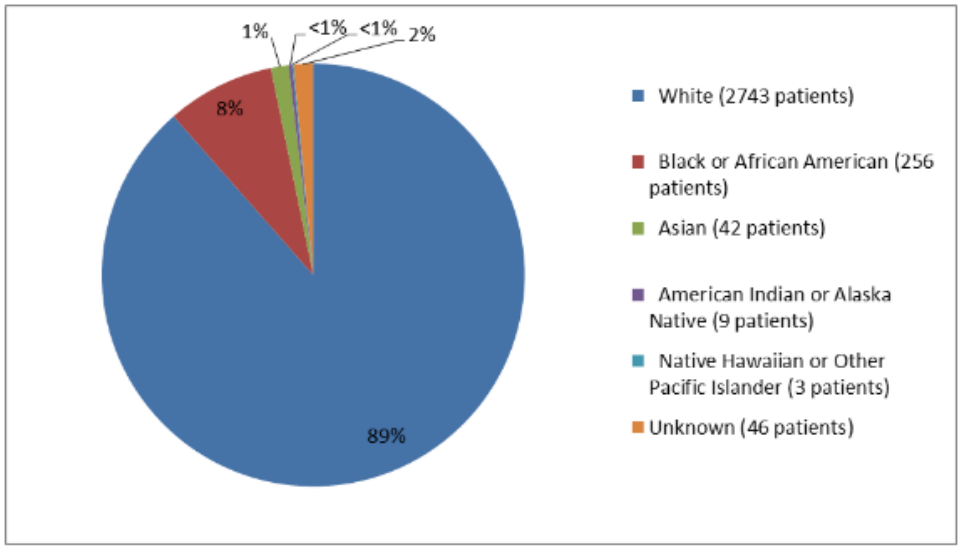
Figure 1. Baseline Demographics by Sex



Source: Company Trial Data

The figure and table below summarize the percentage of patients by race in the clinical trials.

Figure 2. Baseline Demographics by Race



<1%=less than 1%
Source: Company Trial Data

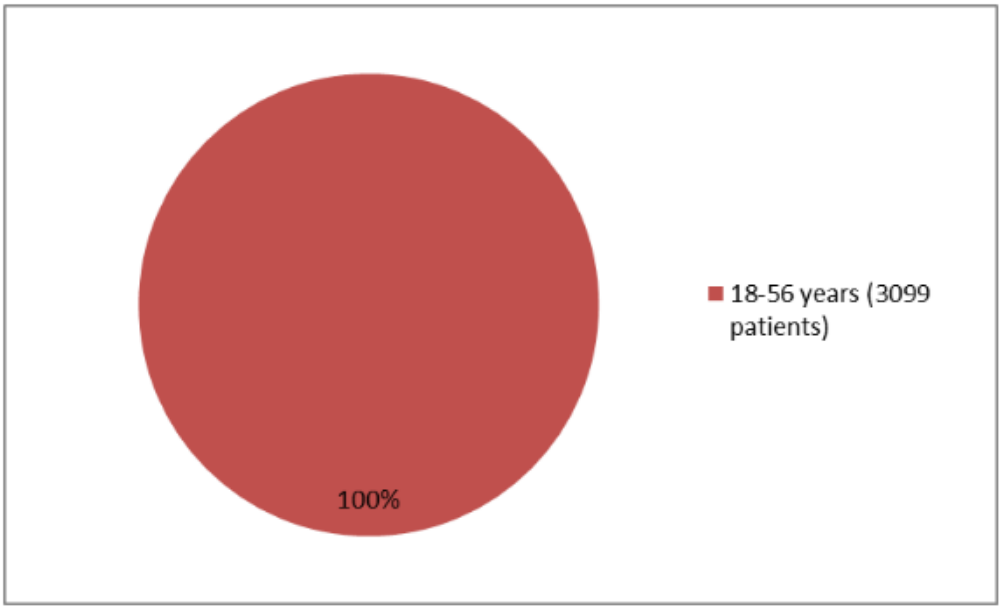
Table 1. Demographics by Race

Race	Number of Patients	Percentage of Patients
White	2743	89%
Black or African American	256	8%
Asian	42	1%
American Indian or Alaska Native	9	less than 1%
Native Hawaiian or Other Pacific Islander	3	less than 1%
Unknown	46	2%

Source: Company Trial Data

The figure below summarizes how many patients by age participated in the clinical trial.

Figure 3. Baseline Demographics by Age



Source: Company Trial Data

MORE INFO

The table below summarizes baseline demographics for the trials (safety population

Table 9. Baseline Demographics

	ADDYI (N=1543)	Placebo (N=1556)	Total (N=3099)
Sex			
Men	0 (0)	0 (0)	0 (0)
Women	1543 (100%)	1556 (100%)	3099 (100%)
Age			
Mean years (SD)	36 (7)	36 (7)	36 (7)
Median (years)	36	36	36
Min, Max (years)	19, 56	18, 54	18, 56
Race			
White	1364 (88%)	1379 (89%)	2743 (89%)
Black or African American	134 (9%)	122 (8%)	256 (8%)
Asian	21 (1%)	21 (1%)	42 (1%)
American Indian or Alaska Native	2 (<1%)	7 (<1%)	9 (<1%)
Native Hawaiian or Other Pacific Islander	1 (<1%)	2 (<1%)	3 (<1%)
Unknown	21 (1%)	25 (2%)	46 (2%)
Ethnicity			
Hispanic or Latino	126 (8%)	114 (7%)	240 (8%)
Not Hispanic or Latino	1394 (90%)	1416 (91%)	2810 (90%)
Unknown	23 (2%)	26 (2%)	49 (2%)
Region			
United States	1115 (72%)	1126 (72%)	2241 (72%)
Canada	112 (7%)	112 (7%)	224 (7%)
Europe	316 (21%)	318 (20%)	634 (21%)

Source: Company Trial Data

How were the trials designed?

There were four trials that compared the side effects of ADDYI to a placebo. Three of these trials also compared the benefits of ADDYI to a placebo. In each trial, patients received ADDYI or a placebo tablet at bedtime for 24 weeks. Neither the patients nor the health care providers knew which treatment was being given until after the trials were completed.

The trials measured the number of satisfying sexual events, the level of sexual desire and the level of distress related to low sexual desire.
MORE INFO

How were the trials designed?

The efficacy of ADDYI for the treatment of HSDD in premenopausal women was evaluated in three 24-week, randomized, double-blind, placebo-controlled trials. The trials included premenopausal women with acquired, generalized HSDD of at least 6 months duration. The patients were treated with either ADDYI 100 mg or placebo once daily at bedtime.

These trials each had two co-primary efficacy endpoints, one for satisfying sexual events and the other for sexual desire. These trials also had a secondary endpoint that evaluated distress related to low sexual desire.

GLOSSARY

CLINICAL TRIAL: Voluntary research studies conducted in people and designed to answer specific questions about the safety or effectiveness of drugs, vaccines, other therapies, or new ways of using existing treatments.
COMPARATOR: A previously available treatment or placebo used in clinical trials that is compared to the actual drug being tested.
EFFICACY: How well the drug achieves the desired response when it is taken as described in a controlled clinical setting, such as during a clinical trial.
PLACEBO: An inactive substance or “sugar pill” that looks the same as, and is given the same way as, an active drug or treatment being tested. The effects of the active drug or treatment are compared to the effects of the placebo.
SUBGROUP: A subset of the population studied in a clinical trial. Demographic subsets include sex, race, and age groups.