

Development of Standardized SAS Macros for Demographic Subgroup Participation in NDAs and BLAs Submitted to FDA’s Center for Drug Evaluation and Research



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Background: The 2012 FDASIA Section 907 required that FDA provide to Congress, and post on FDA’s website, the extent of clinical trial participation and the inclusion of safety and effectiveness data by demographic subgroups (sex, age, race, ethnicity) for marketing applications approved by FDA.¹

To enable the standard representation of demographic subgroup safety and efficacy outcomes in clinical and statistical reviews of new drug applications (NME NDAs and original BLAs), several CDER offices collaborated to develop SAS macros for the tables utilized in these required analyses.

Approach: Tables were developed with statistical programming support, and are to be deployed, with adequate training and analytic support, for all NMEs and original BLAs approved in 2015. The finalized tables will be incorporated in clinical and/or statistical review templates for NDA/BLA reviews, and published on FDA’s website.

This approach required a high level of communication between OCS and OND review divisions. OCS worked with OND to obtain the following information:

- Which study(ies) should be used for efficacy analysis?
- What are the primary endpoint(s) for your review?
 - Which dataset and variables should we use to calculate these endpoint(s)?
- Which study(ies) should be used for safety analysis?
- What was the primary safety analysis for your review? (e.g., any SAE, any TEAE, etc.)
 - Which dataset and variables should we use to calculate the safety analysis?
- Did you use any risk estimators in your review that we should incorporate into our tables? (e.g., Relative Risk, Odd Ratio, Hazard Ratio, Relative Difference, etc.)

Results: Data tables using SAS macros were generated from datasets submitted using SDTM, which were then published on FDA’s website as part of a new initiative titled “Drug Trials Snapshot”.² One example for edoxaban³ is presented in Tables 1-4, along with graphical representation of the data (see Figures 2 & 3).

References:

1. FDASIA. Public Law No 112-144. July 9, 2012.
<http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf>.
2. FDA. Drug Trials Snapshot.
<http://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm>.
3. Drugs@FDA.
[http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.\[“edoxaban”\]](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.[“edoxaban”]).

Disclaimer: The views expressed in this presentation are those of the authors and do not necessarily represent the policy of FDA.

Table 1. Baseline Demographics, Efficacy Population

Demographic Parameters	Treatment Groups			Total (n=21026) 100 (%)
	Warfarin (n=7012) 33.3 (%)	Edoxaban 30mg (15mg DosAdj) (n=7002) 33.3 (%)	Edoxaban 60mg (30mg DosAdj) (n=7012) 33.3 (%)	
Sex				
Male	4383 (62.5)	4284 (61.2)	4353 (62.1)	13020 (61.9)
Female	2629 (37.5)	2718 (38.8)	2659 (37.9)	8006 (38.1)
Age				
Mean years (SD)	70.5 (9.4)	70.6 (9.3)	70.6 (9.5)	70.6 (9.4)
Median (years)	72	72	72	72
Min, Max (years)	27,95	27,95	25,96	25,96
Age Group				
<17 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>=17 - <65 years	1869 (26.7)	1784 (25.5)	1830 (26.1)	5483 (26.1)
>=65 years	5143 (73.3)	5218 (74.5)	5182 (73.9)	15543 (73.9)
>=75 years	2805 (40.0)	2789 (39.8)	2838 (40.5)	8432 (40.1)
Race				
White	5679 (81.0)	5650 (80.7)	5679 (81.0)	17008 (80.9)
Black or African American	88 (1.3)	94 (1.3)	96 (1.4)	278 (1.3)
Asian	963 (13.7)	975 (13.9)	956 (13.6)	2894 (13.8)
American Indian or Alaska Native	16 (0.2)	22 (0.3)	13 (0.2)	51 (0.2)
Native Hawaiian or Other Pacific Islander*	--	--	--	--
Other	265 (3.8)	257 (3.7)	265 (3.8)	787 (3.7)
Missing	0 (0.0)	1 (0.0)	0 (0.0)	1 (0.0)
Ethnicity				
Hispanic or Latino	782 (11.2)	781 (11.2)	764 (10.9)	2327 (11.1)
Not Hispanic or Latino	4476 (63.8)	4476 (63.9)	4511 (64.3)	13463 (64.0)
Missing	1754 (25.0)	1745 (24.9)	1737 (24.8)	5236 (24.9)
Region				
United States	1297 (18.5)	1308 (18.7)	1288 (18.4)	3893 (18.5)
Rest of the World				
Canada	259 (3.7)	242 (3.5)	271 (3.9)	772 (3.7)
Latin America	885 (12.6)	882 (12.6)	884 (12.6)	2651 (12.6)
Europe	3448 (49.2)	3444 (49.2)	3449 (49.2)	10341 (49.2)
Asia Pacific and Africa	1123 (16.0)	1126 (16.1)	1120 (16.0)	3369 (16.0)
*Cells that contain at least 1 but <10 patients are censored.				
Source: Study du176b-c-u301; DM.xpt				

Table 2. Subgroup Analysis, Primary Efficacy Endpoint

Demographic Subgroup	Warfarin (n=7012)		Edoxaban 60mg (30mg DosAdj) (n=7012)	
	n (%/year)	Total, N	n (%/year)	Total, N
Overall Response/All patients	232 (1.50)	232	182 (1.18)	7012
Sex				
Male	144 (1.46)	4383	115 (1.16)	4353
Female	88 (1.55)	2629	67 (1.21)	2659
Age Group				
<17 years	0 (0)	0	0 (0)	0
>=17 - <65 years	36 (0.80)	1869	42 (0.96)	1830
>=65 years	81 (1.53)	2338	65 (1.22)	2344
>=75 years	115 (2.02)	2805	75 (1.31)	2838
Race				
White	171 (1.35)	5679	144 (1.15)	5679
Black or African American		88	2 (1.06)	96
Asian	48 (2.30)	963	30 (1.41)	956
American Indian or Alaska Native	1 (3.10)	16	0 (0.00)	13
Native Hawaiian or Other Pacific Islander*	--	--	--	--
Other	11 (2.00)	265	6 (1.03)	265
Ethnicity*				
Hispanic or Latino	36 (2.24)	782	15 (0.96)	764
Not Hispanic or Latino	140 (1.41)	4476	118 (1.19)	4511
Region				
United States	34 (1.16)	1297	19 (0.67)	1288
Rest of the World				
Canada	8 (1.48)	259	4 (0.68)	271
Latin America	42 (2.33)	885	20 (1.09)	884
Europe	93 (1.20)	3448	104 (1.35)	3449
Asia Pacific and Africa	55 (2.24)	1123	35 (1.41)	1120
*Cells that contain at least 1 but <10 patients are censored.				
*105 (56 Warfarin, 49 Edoxaban) participants did not identify their ethnicity.				
Source: Study du176b-c-u301; DM.xpt and ADJEFFCA.xpt				

Table 3. Baseline Demographics, Safety Population

Demographic Parameters	Treatment Groups			Total (n=21026) 100 (%)
	Warfarin (n=7012) 33.3 (%)	Edoxaban 30mg (15mg DosAdj) (n=7002) 33.3 (%)	Edoxaban 60mg (30mg DosAdj) (n=7012) 33.3 (%)	
Sex				
Male	4383 (62.5)	4284 (61.2)	4353 (62.1)	13020 (61.9)
Female	2629 (37.5)	2718 (38.8)	2659 (37.9)	8006 (38.1)
Age				
Mean years (SD)	70.5 (9.4)	70.6 (9.3)	70.6 (9.5)	70.6 (9.4)
Median (years)	72	72	72	72
Min, Max (years)	27,95	27,95	25,96	25,96
Age Group				
<17 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>=17 - <65 years	1869 (26.7)	1784 (25.5)	1830 (26.1)	5483 (26.1)
>=65 years	5143 (73.3)	5218 (74.5)	5182 (73.9)	15543 (73.9)
>=75 years	2805 (40.0)	2789 (39.8)	2838 (40.5)	8432 (40.1)
Race				
White	5679 (81.0)	5650 (80.7)	5679 (81.0)	17008 (80.9)
Black or African American	88 (1.3)	94 (1.3)	96 (1.4)	278 (1.3)
Asian	963 (13.7)	975 (13.9)	956 (13.6)	2894 (13.8)
American Indian or Alaska Native	16 (0.2)	22 (0.3)	13 (0.2)	51 (0.2)
Native Hawaiian or Other Pacific Islander*	--	--	--	--
Other	265 (3.8)	257 (3.7)	265 (3.8)	787 (3.7)
Missing	0 (0.0)	1 (0.0)	0 (0.0)	1 (0.0)
Ethnicity				
Hispanic or Latino	782 (11.2)	781 (11.2)	764 (10.9)	2327 (11.1)
Not Hispanic or Latino	4476 (63.8)	4476 (63.9)	4511 (64.3)	13463 (64.0)
Missing	1754 (25.0)	1745 (24.9)	1737 (24.8)	5236 (24.9)
Region				
United States	1297 (18.5)	1308 (18.7)	1288 (18.4)	3893 (18.5)
Rest of the World				
Canada	259 (3.7)	242 (3.5)	271 (3.9)	772 (3.7)
Latin America	885 (12.6)	882 (12.6)	884 (12.6)	2651 (12.6)
Europe	3448 (49.2)	3444 (49.2)	3449 (49.2)	10341 (49.2)
Asia Pacific and Africa	1123 (16.0)	1126 (16.1)	1120 (16.0)	3369 (16.0)
*Cells that contain at least 1 but <10 patients are censored.				
Source: Study du176b-c-u301; DM.xpt				

Table 4. Subgroup Analysis, Primary Safety Endpoint

Demographic Subgroup	Warfarin (N=7012)		Edoxaban 60mg (30mg DosAdj) (N=7012)	
	n (%/year)	Total, N	n (%/year)	Total, N
Major Bleed				
Sex				
Male	336 (3.4)	4383	283 (2.8)	4353
Female	188 (3.3)	2629	135 (2.4)	2659
Age Group				
<17 years	0 (0)	0	0 (0)	0
>=17 - <65 years	81 (1.8)	1869	64 (1.4)	1830
>=65 years	443 (4.0)	5143	354 (3.2)	5182
>=75 years	270 (4.7)	2805	224 (3.9)	2838
Race				
White	404 (3.2)	5679	335 (2.7)	5679
Black or African American	8 (4.7)	88	4 (2.0)	96
Asian	86(4.1)	963	67(3.1)	956
American Indian or Alaska Native	0 (0.0)	16	0 (0.0)	13
Native Hawaiian or Other Pacific Islander*	--	--	--	--
Other	26 (4.7)	265	12 (2.0)	265
Ethnicity*				
Hispanic or Latino	62(3.8)	782	45 (2.9)	764
Not Hispanic or Latino	336 (3.3)	4476	277 (2.8)	4511
Region				
United States	133 (4.5)	1297	109 (3.9)	1288
Rest of the World				
Canada	19 (3.5)	259	26 (4.4)	271
Latin America	67 (3.7)	885	48 (2.6)	884
Europe	206 (2.6)	3448	150 (1.9)	3449
Asia Pacific and Africa	99 (4.0)	1123	85 (3.4)	1120
*Cells that contain at least 1 but <10 patients are censored.				
*Missing ethnicity data for 1754 Warfarin and 1737 Edoxaban 60mg (30mg DosAdj) patients.				
Source: Study du176b-c-u301; DM.xpt and BLDDATA.xpt				

Figure 1. Process Flow



Figure 2. Clinical Trial Sex Demographics, edoxaban

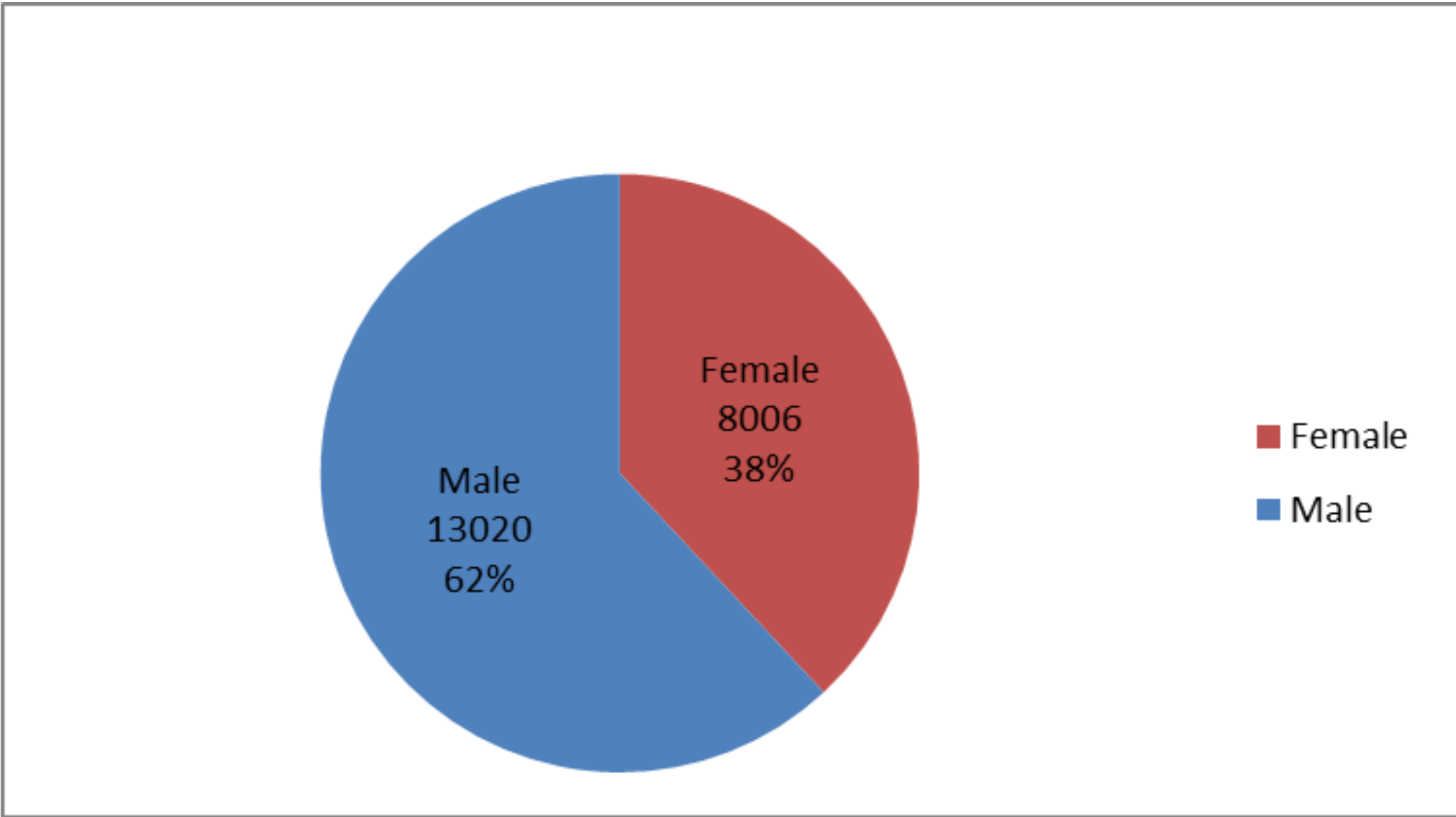
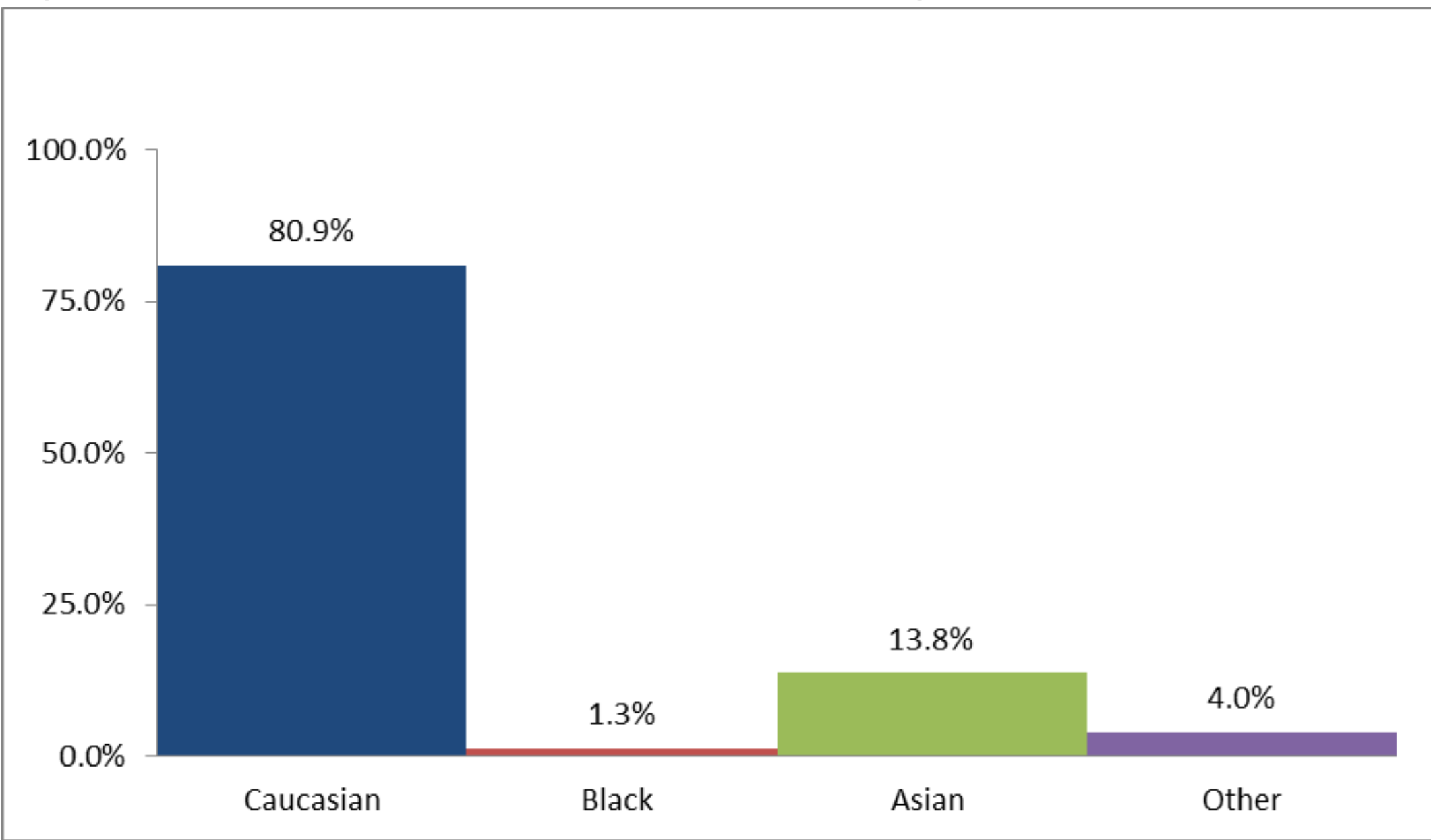


Figure 3. Clinical Trial Race Demographics, edoxaban



Discussion: Consistent summarization of demographic subgroup data from marketing applications will enable high quality data compilation and analyses for demographic subgroup participation in clinical trials. Results of these analyses are expected to support FDA's mission for the review and regulation of drugs for the diverse populations who will use these drugs post-approval. We believe that the SAS macros will facilitate review and generation of the demographic subgroup analyses, and be helpful to ensure consistency of these analyses across marketing applications. To provide transparent results for the patients and healthcare providers, the results are being published on FDA's website.² Integration of biomedical and clinical trials data and IT tools through inter-office collaboration can serve as a model as to how informatics initiatives such as this can inform policy and contribute to the public health.

Abbreviations:
FDA = Food and Drug Administration; CDER = Center for Drug Evaluation and Research; OCS = Office of Computational Science; OND = Office of New Drugs; DNP = Division of Neurology Products; IBM = International Business Machines Corporation; PASE = Professional Affairs and Stakeholder Engagement; OCD = Office of the Center Director; OB = Office of Biostatistics; DBII = Division of Biostatistics II; OTS = Office of Translational Sciences; RDP = Rare Diseases Program; FDASIA = Food and Drug Administration Safety and Innovation Act; NME = new molecular entity; NDA = new drug application; BLA = biologics license application; SAE = serious adverse event; TEAE = treatment-emergent adverse event; SDTM = Study Data Tabulation Model