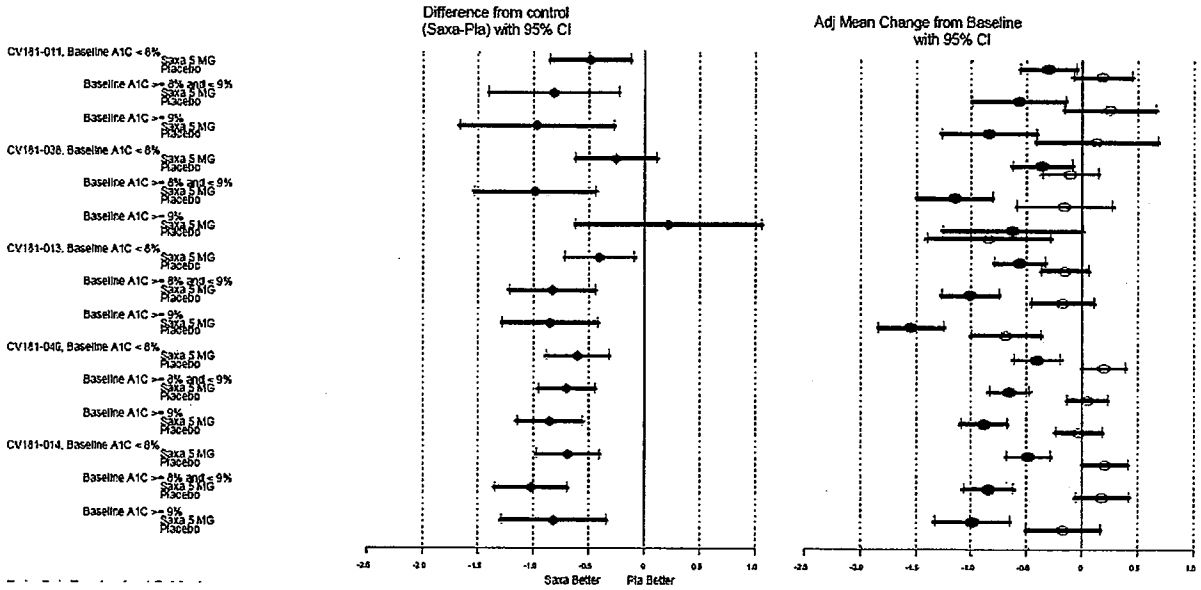
Baseline A1c

Although shown to be effective across baseline A1c subgroups, saxagliptin 5 mg was shown in most studies to produce numerically greater reductions from baseline for those with higher baseline A1c. The treatment-by-subgroup interaction p-value was <0.1 for in 3 of the 6 studies. As seen in Figure 6.6 below, the trend of greater reduction in A1c in subjects with higher baseline A1c values was not seen in Study CV181038. The Sponsor did not present this analysis for Study CV181039, however noted that a statistically significant interaction was not generated because a similar pattern of greater reduction in A1c was seen in the active-control group.

Figure 6.6. Plot of Adjusted Mean Change from Baseline in A1c and 95% Confidence Intervals at Week 24 for Saxagliptin 5 mg Groups in Each Protocol, by Baseline A1c Subgroups



Source: Summary of Clinical Efficacy, Figure 3.3A

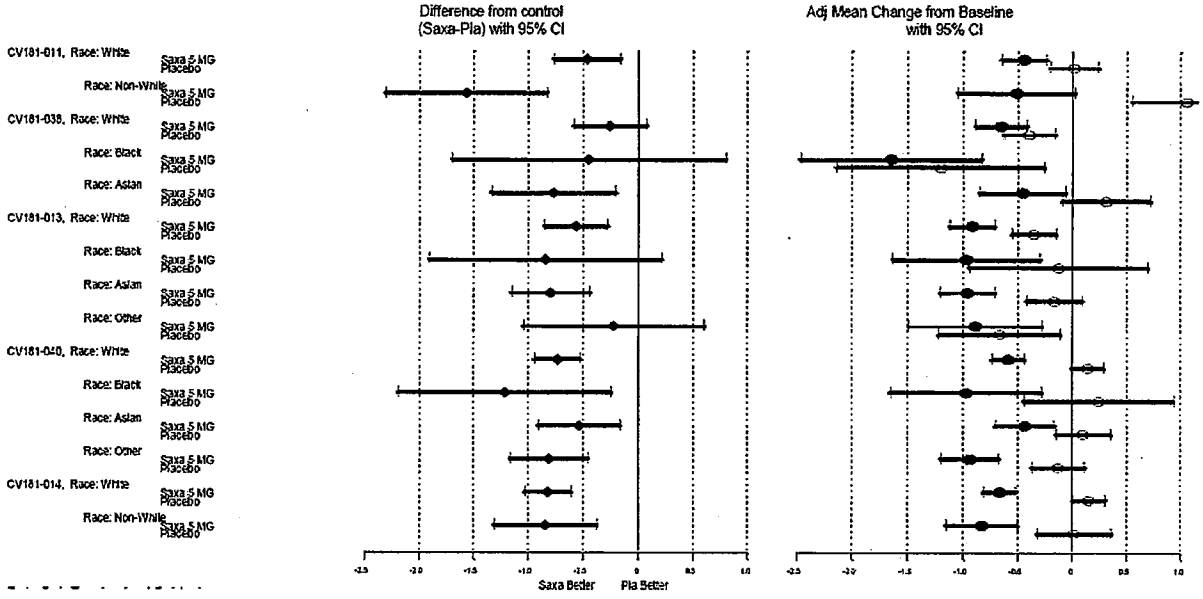
Race

In the Core Phase 3 studies, the majority of subjects enrolled were white. P-values for treatment-by-race interactions were <0.1, however the Sponsor asserts that this is due to variability in A1c responses in the placebo or active-control treatment groups. The point estimate of the adjusted change from baseline in A1c for the saxagliptin 5 mg group was fairly consistent for race subgroups across studies, and the 95% CI crossed zero only for nonwhite subjects in CV181011 (n=13, right panel in Figure 6.7 below).

The treatment-by-race subgroup interaction p-value was <0.1 in the trials with treatment-naïve subjects (CV181011, CV181038, and CV181039). It is unclear why this was seen. Overall, however, it appears that no conclusions regarding the effect of race in saxagliptin treatment can be made.

Reviewer comment: According to Ms. Mele's analysis of HbA1c treatment effect by race, although Asians were a minority of enrolled subjects (highest enrollment was 15% in Study CV181039), two studies (CV181011 and CV181039) produced significant interactions. Given this, the clinical implications for the treatment of Asians, including PK exposure, and safety, should be considered.

Figure 6.7. Plot of Adjusted Mean Change from Baseline in A1c and 95% Confidence Intervals at Week 24 for Saxagliptin 5 mg Groups in Each Protocol, by Race Subgroups

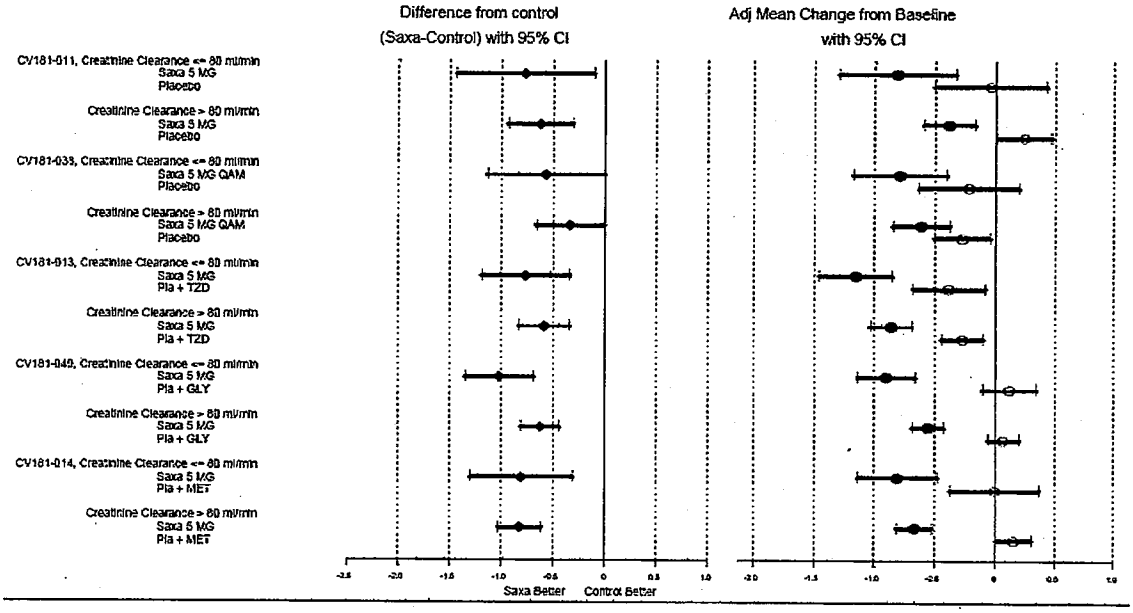


Source: Summary of Clinical Efficacy, Figure 3.3B

Baseline Creatinine Clearance

The interaction p-values were >0.1 in both monotherapy trials and <0.1 in 2 of the 3 add-on combination trials. This may be explained by a greater dose-response separation in subjects in the subgroups with baseline creatinine clearance ≤80 mL/min in the add-on combination studies. The saxagliptin 5 mg group had a greater adjusted mean reduction in A1c at Week 24 than the 2.5 mg groups in the add-on combination studies. However, the change from baseline A1c in the control group was similar between the subgroups. As seen in Figure 6.8 below, the control-corrected adjusted mean A1c reduction and the adjusted mean A1c reduction was consistently greater for saxagliptin 5 mg in the subgroup with creatinine clearance ≤80 mL/min. The Sponsor hypothesizes that reduced renal clearance of insulin (saxagliptin increases post-prandial insulin secretion) may contribute to these findings.

Figure 6.8. A1c Changes from Baseline in Subgroups Based on Creatinine Clearance in Monotherapy and Add-on Therapy Studies



Source: Summary of Clinical Efficacy, Figure 3.3D

Other subgroups

Several subgroups, including gender, had interaction p-values <0.1 in only one trial; each of these trials involved treatment-naïve subjects.

For age and baseline BMI, there were no analyses with an interaction p-value <0.1. Regarding age, it is important to note that the percentage of subjects >75 years old in the Core Phase 3 studies was low (1.4%). Interpretation of this specific subgroup analysis is therefore limited.

Overall, subgroup analyses did not reveal any unexpected conclusions. Greater reductions in A1c associated with higher baseline A1c is typically seen with other drugs used for the treatment of diabetes.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In Phase 1 and 2 studies, saxagliptin 5 mg was associated with greater inhibition of plasma DPP4 activity at the trough of the dosing interval compared to 2.5 mg. In the Phase 2b study, the 5 mg dose also resulted in maximal reductions in A1c and fasting serum glucose (Section 4.4). The Phase 3 studies confirmed the effects of saxagliptin 5 mg on A1c. A major strength of the

Sponsor's clinical development program was the incorporation of multiple doses in the Phase 3 studies, allowing for a more thorough evaluation of the dose chosen from Phase 2.

In the Phase 3 studies, saxagliptin 10 mg did not result in incremental benefit, and in fact, was associated with certain adverse effects not observed with the 5 mg dose (Section 7).

The benefit of 5 mg versus 2.5 mg was adequately demonstrated in the primary efficacy endpoint:

- With the exception of the monotherapy studies, subjects in the saxagliptin 5 mg groups demonstrated greater decreases from baseline in A1c at 24 weeks versus the 2.5 mg groups. In both monotherapy studies, subjects in the 2.5 mg and 5 mg groups demonstrated similar A1c reductions.

Reviewer comment: In Study CV181038, the decreases from baseline in A1c at 24 weeks for the 2.5 mg and 5 mg groups were -0.71% and -0.66%, respectively. As mentioned earlier in this Review, this study had the smallest number of subjects per dose group and therefore was more prone to confounding factors or chance findings. This one exception to the otherwise demonstrated benefit of 5 mg over 2.5 mg should be viewed with this study limitation.

When analyzing secondary endpoints, the benefit of 5 mg versus 2.5 mg was also generally demonstrated.

- In all studies, the saxagliptin 5 mg group had a greater reduction in postprandial glucose AUC versus the 2.5 mg group, although differences in the monotherapy trials were modest.
- The proportion of subjects who achieved a glycemic response of A1c<7% was higher in the saxagliptin 5 mg groups versus the 2.5 mg groups in one of the monotherapy studies and the add-on combination study to metformin. Minimal differences were observed in the other monotherapy study and the 2 add-on combination studies.
- In the add-on combination studies only, the saxagliptin 5 mg group had greater decreases from baseline in FPG than the saxagliptin 2.5 mg groups, although differences were modest for the add-on to sulfonylurea trial and the 2.5 mg and 5 mg groups reduced FPG to a similar extent in the monotherapy trials.

As discussed in Section 4.4, while the 5 mg per day dose appears to be the optimal dose in most subjects, those with moderate or severe renal insufficiency are recommended a dose adjustment to 2.5 mg.

Finally, the Sponsor examined subgroups to determine if there was a particular group of subjects in which the greater efficacy of the 5 mg dose versus the 2.5 mg dose was observed. This was seen in the subjects with creatinine clearance ≤80 ml/min in the add-on studies, with an approximately 2-fold difference in the reduction from baseline A1c at the 5 mg dose compared to 2.5 mg. This was previously discussed in Section 6.1.7.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Each Core Phase 3 study included an extension phase of at least 12 months to allow for additional safety and efficacy data. These periods were ongoing at the time of NDA submission, and therefore only interim results were submitted. Subjects remained in the treatment group to which they were assigned in the ST period, although some required rescue in addition to their randomized treatment.

Despite these long-term extensions, the Phase 3 studies were not designed to specifically look at persistence of drug effect beyond Week 24. LOCF methodology is used in the Sponsor's analyses, and this is problematic, particularly if subjects were rescued early in the study. There are limitations to the utility of such analyses. Sample sizes by the end of the evaluated periods are low. For example, in Study CV181038, approximately 10 subjects each remained in the treatment groups. Such low sample sizes limit a meaningful interpretation and extrapolation to a wider population.

6.1.10 Additional Efficacy Issues/Analyses

7 Review of Safety

Safety Summary

In general, saxagliptin appears to have a favorable safety profile. The safety database from the Phase 2b/3 program is based on exposure of 3422 subjects. Of these, 2642 subjects were exposed to study drug for ≥24 weeks and 1080 subjects were exposed for ≥52 weeks.

Issues that will be discussed in this section of the Review include:

Deaths and Major Adverse Cardiovascular Events (MACE): There were no increased deaths in saxagliptin-treated subjects. As discussed in depth in this Section, although the saxagliptin clinical development program did not prospectively plan an evaluation of MACE, a retrospective and comprehensive analysis did not reveal an increased frequency of MACE events among saxagliptin-treated subjects. This was also the subject of an Advisory Committee meeting, discussed at length in Section 9.3.

Serious Adverse Events: There were no concerning signals of specific serious adverse events among saxagliptin-treated subjects.

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