昂格莎膜衣錠 2.5 毫克，5 毫克

Onglyza® (saxagliptin) Film-coated Tablets 2.5 mg, 5 mg

本藥須由醫師處方使用
2.5 毫克　衛署藥輸字第 025220 號
5　毫克　衛署藥輸字第 025221 號

1　適應症

第二型糖尿病。[參見*臨床試驗 (14)*]

1.1　使用上重要的限制

ONGLYZA 不適用於第一型糖尿病病人，或治療糖尿病酮酸血症，因為它對這些狀況無效。

2　用法用量

2.1　建議劑量

ONGLYZA 的建議劑量為每日一次 2.5 毫克或 5 毫克，可單獨使用亦可與 metformin、sulfonylurea、PPARγ作用劑 (如 thiazolidinedione)、胰島素 (併用或不併用 metformin)、metformin 加一種 sulfonylurea 合併使用或 metformin 加上 dapagliflozin 合併使用，做為附加於飲食控制及運動之外的治療藥物，藉以改善第二型糖尿病病人的血糖控制效果。ONGLYZA 可與食物併服或空腹服用。[參見*臨床試驗 (14)*]

2.2　腎功能不全病人之劑量

對 eGFR ≥ 45mL/min/1.73 m^2 的病人，不建議調整 ONGLYZA 劑量。

對 eGFR < 45mL/min/1.73 m^2 (包括中度或重度腎功能不全的病人或需要接受血液透析的末期腎病 (ESRD)) 的病人 [參見*臨床藥理學 (12.3) 與臨床試驗 (14.2)*]，ONGLYZA 劑量為每日一次 2.5 毫克 (不論是否用餐)。ONGLYZA 應在血液透析後給藥。ONGLYZA 未曾針對腹膜透析病人進行研究。

由於腎功能不全病人的 ONGLYZA 劑量最高為 2.5 毫克，因此建議開始 ONGLYZA 治療前應先評估腎功能，此後亦應定期進行評估。

2.3　與CYP3A4/5 的強力抑制劑併用時之劑量調整

與強效的cytochrome P450 3A4/5 (CYP3A4/5) 抑制劑 (如 ketoconazole、atazanavir、clarithromycin、indinavir、itraconazole、nefazodone、nelfinavir、ritonavir、saquinavir和telithromycin) 合併使用時，ONGLYZA 劑量為每日一次 2.5 毫克。[參見*藥物交互作用 (7.1) 及臨床藥理學 (12.3)*]

2.4　與胰島素分泌刺激劑(例如磺脲類Sulfonylurea)或胰島素同時使用

當 ONGLYZA 與胰島素分泌刺激劑 (如磺脲類 sulfonylurea) 或胰島素同時使用，胰島素分泌刺激劑或胰島素的劑量可能需要降低，盡量減少低血糖的風險。[參見*警語及注意事項 (5.3)*]

3　劑型與劑量

- ONGLYZA (saxagliptin) 5mg：為粉紅色、兩面凸出、圓形膜衣錠，一面印有「5」，另一面印有「4215」之藍色字樣。

- ONGLYZA (saxagliptin) 2.5 mg：為淺黃至淡黃色、兩面凸出、圓形膜衣錠，一面印有「2.5」，另一面印有「4214」之藍色字樣。

4 禁忌症

ONGLYZA 禁用於對於 ONGLYZA 曾發生嚴重過敏反應，如過敏性反應 (anaphylaxis)、血管性水腫、或剝落性皮膚病；或是對於本品之任何成分過敏者。[參見*警語及注意事項 (5.4)* 及*不良反應 (6.2)*]

5 警語及注意事項

5.1 胰臟炎

上市後曾經有服用 ONGLYZA 的病人發生急性胰臟炎的報告。在一個收錄有動脈粥狀硬化心血管疾病 (Atherosclerotic Cardiovascular Disease, ASCVD) 或有 ASCVD 多種危險因子的受試者的心血管預後試驗 (SAVOR 試驗) 中，被確診急性胰臟炎病例的，在接受 ONGLYZA 的病人中有 17/8240 例 (0.2%)，而在接受安慰劑的病人中有 9/8173 例 (0.1%)。其中原本就有胰臟炎危險因子的，在接受 ONGLYZA 的病人中有 88% (15/17)，在接受安慰劑的病人中則是 100% (9/9)。

開始服用 ONGLYZA 之後，要仔細觀察病人有無胰臟炎的症狀和徵象。如果懷疑是胰臟炎，要迅速停用 ONGLYZA，且應開始適當的處置。有胰臟炎病史的病人使用 ONGLYZA 時，是否會增加胰臟炎的風險仍未知。

5.2 心衰竭

在收錄有 ASCVD 或有 ASCVD 多種危險因子的受試者的心血管預後試驗 (SAVOR 試驗) 中，相較於隨機接受安慰劑的病人 (228/8212, 2.8%)，有較多隨機分配到 ONGLYZA 的病人因心衰竭住院 (289/8280, 3.5%)。發生首次事件所需時間分析顯示，ONGLYZA 組因心衰竭住院的風險較高 (預估風險比：1.27；95% CI：1.07, 1.51)。有心衰竭病史的病人和腎功能不全病人因心衰竭住院的風險較高，不論治療分配為何。

在開始治療心衰竭風險較高病人前，要考慮 ONGLYZA 的風險和效益。治療期間觀察病人有無心衰竭的表徵和症狀。告知病人心衰竭的典型症狀，並且立即通報此類症狀。如果發生心衰竭，評估並按照目前的標準療法處理，且考慮停用 ONGLYZA。

5.3 併用Sulfonylurea或胰島素造成之低血糖

當 ONGLYZA 與磺脲類 (sulfonylurea) 或與胰島素等會造成低血糖的藥物併用時，低血糖發生率增加，比安慰劑與磺脲類 (sulfonylurea) 或與胰島素併用時為高 [參見*不良反應 (6.1)*]。因此與 ONGLYZA 併用時，胰島素分泌刺激劑或胰島素的劑量可能需要降低，以盡量減少低血糖的風險。[參見*用法用量 (2.4)*]

5.4 過敏反應

上市後有使用 ONGLYZA 治療的病人發生嚴重過敏反應的報告，這些反應包括過敏性反應、血管性水腫、和剝落性皮膚病。這些不良反應在開始 ONGLYZA 治療的頭三個月內出現，有些發生在投予第一劑之後。如果懷疑發生嚴重過敏反應，應停用 ONGLYZA，評估其他可能的導致因素，並以其他的糖尿病治療替代。[參見*不良反應 (6.2)*]

對於任何二肽基肽酶4 (DPP4) 抑制劑有血管性水腫反應病史之病人應小心使用，因此類病人是否易於對 ONGLYZA 產生血管性水腫反應仍未知。

5.5 嚴重和導致無法行動的關節痛

雙肽胜肽酶-4 (DPP-4) 抑制劑的上市後報告中曾有嚴重和造成行動不便之關節疼痛案例。這些病人是在開始用藥後第一天或幾年後發生關節疼痛症狀。病人停藥後則可緩解症狀。部分病人於重新服用相同的藥物或不同的 DPP-4 抑制劑時症狀會復發。在使用 DPP-4 抑制劑的病人，需考慮 DPP-4 抑制劑可能為導致嚴重且持續性關節疼痛的原因，考慮適時停藥並避用其他 DPP-4 抑制劑。

5.6 類天皰瘡

曾有使用DPP-4抑制劑發生類天皰瘡並需要住院治療的上市後案例。在通報的案例中，病人通常可在局部性或全身性的免疫抑制治療及停止使用DPP-4抑制劑後復原。應告知病人在接受ONGLYZA治療時，通報發生水皰或糜爛情況。如懷疑是類天皰瘡，應考慮停止使用ONGLYZA並轉介至皮膚科醫生診斷及接受適當的治療。

5.7 大血管事件

臨床試驗中並沒有確切的證據足以證明 ONGLYZA 可降低大血管事件的風險。

6 不良反應

下列嚴重不良反應在下方或仿單其他部分有更詳細的討論：

- 胰臟炎 [參見*警語和注意事項 (5.1)*]
- 心衰竭 [參見*警語和注意事項 (5.2)*]
- 併用 Sulfonylurea 或胰島素造成之低血糖 [參見*警語和注意事項 (5.3)*]
- 過敏反應 [參見*警語和注意事項 (5.4)*]
- 嚴重和導致無法行動的關節痛 [參見*警語和注意事項 (5.5)*]
- 類天皰瘡 [參見*警語和注意事項 (5.6)*]

6.1 臨床試驗經驗

臨床試驗是在各種不同的條件下所進行，因此藥物臨床試驗中觀察到的不良反應比例，無法與其他臨床試驗的比例直接比較，也未必與臨床實務上的觀察結果相符。

療效試驗之不良反應

表 1 中的數據是源自於 5 項安慰劑對照臨床試驗的合併分析結果 [參見*臨床研究 (14)*]。表中顯示的數據反映 882 名使用 ONGLYZA 且平均使用期間為 21 週的病人。這些病人的平均年齡為 55 歲，1.4 % 為 75 歲以上，48.4 % 為男性。67.5 % 為白人，4.6 % 為黑人或非裔美國人，17.4 % 為亞洲人，其他 10.5 % 和 9.8 % 為西班牙裔或拉丁美洲裔。基準期時受試族群的糖尿病病程平均 5.2 年，平均 HbA1c 為 8.2 %。基準期時 91 % 的病人腎功能被估計為正常或輕度腎功能不全 (eGFR ≥ 60mL/ min/1.73m^2)。

表 1 顯示與使用 ONGLYZA 有關的常見不良反應，但不包括低血糖。這些不良反應在 ONGLYZA 治療組比安慰劑組更常見，且在 ONGLYZA 治療組病人中的發生率至少是 5 %。

表 1：在安慰劑對照試驗中*，ONGLYZA 5 mg 治療組發生率 ≥5 % 且高於安慰劑組的不良反應

	病人人數 %	
	ONGLYZA 5 mg N=882	**安慰劑 N=799**
上呼吸道感染	7.7	7.6
泌尿道感染	6.8	6.1
頭痛	6.5	5.9

* 這 5 項安慰劑對照試驗包含兩項單一療法試驗，以及下列藥物的附加合併療法試驗各一項：metformin、thiazolidinedione 及 glyburide。此表說明 24 週的數據，不論有無血糖救援。

ONGLYZA 2.5 mg 治療組，頭痛 (6.5%) 是唯一發生率 ≥5 % 且高於安慰劑組的不良反應。

在本合併分析中，ONGLYZA 2.5 mg 組或 5 mg 治療組發生率 ≥2 % 且高於安慰劑組 ≥1 % 的不良反應包括：鼻竇炎 (各為 2.9%、2.6%、1.6%)，腹痛 (各為 2.4%、1.7%、0.5%)，胃腸炎 (各為 1.9%、2.3%、0.9%)，嘔吐 (2.2%、2.3%、1.3%)。

在 TZD 的附加試驗中，ONGLYZA 5 mg 組的周邊水腫發生率高於安慰劑組 (各為 8.1 %、4.3 %)。ONGLYZA 2.5 mg 組周邊水腫發生率為 3.1 %。周邊水腫的不良反應，皆未造成試驗藥物停藥。單一療法中，ONGLYZA 2.5 mg 組及 ONGLYZA 5 mg 組相對於安慰劑組，周邊水腫發生率各為 3.6 %、2 %、3 %；併用 metformin 做為附加治療時，各為 2.1 %、2.1 %、2.2 %；併用 glyburide 做為附加治療時，各為 2.4 %、1.2 %、2.2 %。

ONGLYZA (2.5 mg、5 mg、10 mg 的分析結果) 與安慰劑對照組的骨折發生率，各為每百人年 (patient-years) 1.0 及 0.6。10mg 的劑量不是核准劑量。使用 ONGLYZA 病人的骨折發生率，並不會隨時間而提高。尚未確定 ONGLYZA 的確會導致骨骼方面的不良影響，非臨床試驗也並未發現此一現象。

臨床試驗中，發生一血小板減少病例，經診斷為自發性血小板缺乏紫斑症，該案例與 ONGLYZA 用藥的關係不明。

在 ONGLYZA 2.5 mg 治療組、ONGLYZA 5 mg 治療組及安慰劑組，病人因不良事件而停止治療的比例各為 2.2%、3.3% 及 1.8%。與提早停藥相關的最常見不良事件 (ONGLYZA 2.5 mg 組或 5 mg 組至少有 2 名以上病人發生) 包括淋巴球缺少症 (各為 0.1%、0.5% 對 0%) 、紅疹 (0.2%、0.3% 對 0.3%) 、血中肌酸酐升高 (0.3%、0% 對 0%) 、血中肌酸磷酸激酶升高 (0.1%、0.2% 對 0%)。

與胰島素併用之不良反應

在胰島素的附加試驗中 [參見*臨床試驗 (14.1)*]，不良事件 (包括嚴重不良事件和因不良事件停藥) 的發生率，除了經證實的低血糖之外，ONGLYZA 組和安慰劑組之間是相似的 [參見*不良反應 (6.1)*]。

未曾接受治療之第二型糖尿病病人與 Metformin 併用的不良反應

表 2 顯示在另一項為期 24 週，併用 ONGLYZA 與 metformin 作為起始治療之活性藥物對照研究中，≥5% 病人通報 (不論試驗主持人對因果關係的評估為何) 的不良反應。

表 2：未曾接受治療的病人併用 ONGLYZA 及 Metformin 作為起始治療：ONGLYZA 5 mg 合併 Metformin 治療組，發生率 ≥5 %的不良反應而且發生率高於 Metformin 單一治療組

	病人人數 (%)	
	ONGLYZA 5 mg + Metformin*	**Metformin***
	N=320	**N=328**
頭痛	24 (7.5)	17 (5.2)

鼻咽炎	22 (6.9)	13 (4.0)

* Metformin 起始劑量每天 500 mg，逐漸調高至每天 2000 mg 的最高劑量。

低血糖

低血糖不良反應是根據所有包括病人自訴的低血糖事件，並未要求血糖測量，有些病人則是血糖正常，因此不可能確定這些報告全數反映了真正的低血糖。

在 glyburide 附加試驗中，ONGLYZA 2.5 mg 組和 ONGLYZA 5 mg 組的低血糖總發生率 (13.3 % 及 14.6 %) 高於安慰劑組 (10.1 %)。本試驗中，經證實的低血糖定義為低血糖症狀連同指尖血糖值 ≤ 50 mg/dL，其發生率在 ONGLYZA 2.5 mg 組是 2.4 %，ONGLYZA 5 mg 組是 0.8 %，安慰劑組是 0.7 % [參見 *警語及注意事項 (5.3)*]。單一使用 ONGLYZA 2.5 mg、5 mg、安慰劑的低血糖發生率各為 4.0 %、5.6 %、4.1 %；併用 metformin 的合併治療，低血糖發生率各為 7.8 %、5.8 %、5 %；併用 TZD 的發生率各為 4.1 %、2.7 %、3.8 %。未曾接受治療的病人使用 ONGLYZA 5 mg 併用 metformin 後，低血糖發生率是 3.4 %，單獨使用 metformin 的病人是 4.0 %。

在針對單獨使用 metformin 控制不佳的病人，比較 ONGLYZA 5 mg 和 glipizide 附加治療的活性藥物對照試驗中，低血糖的發生率在 ONGLYZA 5 mg 組是 3 % (13名病人發生19起事件)，glipizide 組是 36.3 % (156名病人發生750起事件)。ONGLYZA 治療組沒有人通報經證實的低血糖症狀 (連同指尖血糖值 ≤ 50 mg/dL)，而 glipizide 治療組有 35人 (8.1%) (p<0.0001)。

在胰島素的附加試驗中，低血糖的總發生率在 ONGLYZA 5 mg 組是 18.4 %，安慰劑組是 19.9 %。然而，經證實的症狀性低血糖 (伴有指尖血糖值 ≤ 50 mg/dL) 在 ONGLYZA 5 mg 組的發生率 (5.3%) 比安慰劑 (3.3%) 高。

在 metformin 加 sulfonylurea 的附加試驗中，低血糖的總發生率在 ONGLYZA 5 mg 組是 10.1 %，安慰劑組是 6.3 %。ONGLYZA 治療組有 1.6 % 病人，但安慰劑組沒有人通報經證實的低血糖症狀 [參見 *警語及注意事項 (5.3)*]。

過敏反應

過敏相關的事件，如蕁麻疹、臉部水腫，5 項試驗合併的分析通報，至第 24 週時，使用 ONGLYZA 2.5 mg、5 mg、安慰劑的發生率各為 1.5 %、1.5 %、0.4 %。服用 ONGLYZA 的病人發生的過敏病例，均不需住院治療，試驗主持人亦認為無威脅生命之虞。在這項合併分析中，有一名接受 ONGLYZA 用藥治療的病人，因全身性的蕁麻疹與臉部水腫而停藥。

腎功能不全

在 SAVOR 試驗，與腎功能不全有關的不良反應，包括實驗室檢驗數值變化 (即，與基準期相比，血清肌酸酐加倍且大於 6 mg/dL)，在 ONGLYZA 治療組有 5.8 % 病人 (483/8280) 通報，安慰劑組有 5.1 % 病人 (422/8212) 通報。在 ONGLYZA 治療組與安慰劑組，最常見的不良反應分別包括腎功能不全 (2.1 % 對 1.9 %)、急性腎衰竭 (1.4 % 對 1.2 %) 和腎衰竭 (0.8 % 對 0.9 %)。從基準期到治療結束時，ONGLYZA 治療組病人的 eGFR 平均降低 2.5 mL/min/1.73m^2，安慰劑組病人的平均降低 2.4 mL/min/1.73m^2。隨機分配到 ONGLYZA 治療組的受試者中，eGFR 從 > 50 mL/min (即正常或輕度腎功能不全) 下降到 ≤ 50 mL/min (即中度或重度腎功能不全) 的受試者 (421/5227, 8.1 %) 比隨機分配到安慰劑組多 (344/5073, 6.8 %)。有腎臟不良反應通報的受試者比例隨基準期腎功能惡化程度和年齡增加而增加，不論治療分配為何。

感染

到目前為止，在 ONGLYZA 的非盲性對照臨床試驗資料庫中，4959 名接受 ONGLYZA 治療的病人已有 6 例 (0.12 %) 結核病的通報 (每年每 1000 名病人有 1.1 例)，而在 2868 名接受比較藥物治療的病人卻無結核病通報。這 6 個結核病案例有 2 例經實驗室檢驗確診；其餘病例的資料有限或被推定診斷為結核病。這 6 個病例都不是在美國或西歐發生的。一例發生在加拿大，這名原籍為印尼的病人最近去過印尼。直到通報結核病之前，saxagliptin 治療持續了 144 天到 929 天。四起病例的治療後淋巴球計數都在參考範圍之內。一名病人在開始使用 ONGLYZA 之前有淋巴球減少症，這種情況在整個 ONGLYZA 治療期間保持穩定。最後一名病人大約在通報結核病之前四個月，有一次淋巴球計數低於正常值。沒有與使用 ONGLYZA 有關的自發性肺結核通報。因果關係尚未建立，至今累積的病例太少，無法確定結核病是否與使用 ONGLYZA 有關。

到目前為止，在 ONGLYZA 的非盲性對照臨床試驗資料庫中，有一名接受 ONGLYZA 治療的病人可能發生伺機性感染，他在接受 ONGLYZA 治療約 600 天後發生疑似食物中毒的致死性沙門桿菌敗血症。沒有與使用 ONGLYZA 有關的伺機性感染通報。

生命徵象

接受 ONGLYZA 的病人，其生命徵象未出現具有臨床意義的變化。

實驗室檢驗

絕對淋巴球計數

ONGLYZA 治療組，平均絕對淋巴球計數出現劑量相關的減低現象。從涵蓋五項安慰劑對照臨床研究的綜合分析觀察到，使用 ONGLYZA 5 mg、10 mg 的病人，平均絕對淋巴球計數從約 2200 cells/microL 的基礎值，在用藥第 24 週時，相較於安慰劑，每微升的平均細胞數各減少 100 及 120。ONGLYZA 5 mg 併用 metformin 與單用 metformin 相較，也觀察到類似現象。ONGLYZA 2.5 mg 組相對於安慰劑組並未出現差異。在 ONGLYZA 2.5 mg、5 mg、10 mg、安慰劑各組，淋巴球絕對計數值低於每微升 750 細胞數的病人人數，比例各為 0.5 %、1.5 %、1.4 %、0.4 %。雖然部份病人再度用藥會導致淋巴球數值再次下降，最後必須停藥，但對大多數的病人而言，重複使用 ONGLYZA 並不會導致淋巴球下降的情形復發。淋巴球計數降低未伴隨臨床上有意義的不良反應。10 mg 的劑量不是核准劑量。

在 SAVOR 試驗觀察到，相較於安慰劑，使用 ONGLYZA 的病人淋巴球計數平均下降約 84 cells/microL。在 ONGLYZA 組和安慰劑組，淋巴球絕對計數值下降至 ≤750 cells/microL 的病人比例分別為1.6 % (136/8280) 和1.0 % (78/8212)。

淋巴球計數低於安慰劑組，其臨床意義不明。臨床上有必要時，例如發生罕見或長期感染，應量測淋巴球數值。ONGLYZA 對淋巴球異常 (如 HIV) 病人的淋巴球計數影響，目前不詳。

6.2 上市後經驗

上市後使用 ONGLYZA 發現額外的不良反應。因為這些不良反應屬於自發性通報，病人總數不詳，通常難以可靠的評估這些不良反應的頻率或確定與用藥的因果關係。

- 過敏反應包括過敏性反應、血管性水腫、及剝落性皮膚病 [參見*禁忌 (4)* 及*警語及注意事項 (5.4)*]
- 胰臟炎 [參見*警語及注意事項 (5.1)*]
- 嚴重和導致無法行動的關節痛 [參見*警語及注意事項 (5.5)*]
- 類天皰瘡 [參見*警語及注意事項 (5.6)*]

7 藥物交互作用

7.1 CYP3A4/5酵素的強效抑制劑

Ketoconazole 會顯著增加 saxagliptin 的暴露劑量。其他強效的 CYP3A4/5 抑制劑 (如 atazanavir、clarithromycin、indinavir、itraconazole、nefazodone、nelfinavir、ritonavir、saquinavir、telithromycin) 預期也會導致類似的 saxagliptin 上升現象。因此，如果併用強效的 CYP3A4/5 抑制劑，ONGLYZA 劑量應限制在 2.5 mg。[參見*用法用量 (2.3) 及臨床藥理學 (12.3)*]

8 特殊族群之使用

8.1 懷孕

風險摘要

懷孕婦女使用 ONGLYZA 的資料有限，不足以判斷對於重大先天性缺陷或流產的藥物相關風險。在懷孕期間糖尿病控制不佳對於母親和胎兒有相關風險 [見*臨床評估事項*]。

當懷孕大鼠和兔子在器官形成期間、以及懷孕及哺乳大鼠在產前和產後施用 saxagliptin，在排除母體毒性因素後，均未顯示對發育有不良影響 [見*試驗資料*]。

患有妊娠前糖尿病且 HbA1c > 7 的女性，其重大先天性缺陷的預估背景風險約為 6 % 至 10 %；而 HbA1c > 10 的女性，則曾通報高達 20 至 25 %。有關特定族群發生流產的預估背景風險尚不清楚。在美國一般族群，臨床確認的懷孕中，發生重大先天性缺陷和流產的預估背景風險分別為 2 至 4 % 和 15 至 20 %。

臨床評估事項

疾病相關的母體和/或胚胎/胎兒風險

懷孕中糖尿病控制不佳增加母體罹患糖尿病酮酸症、子癇前症、自發性流產、早產、死胎及分娩併發症的風險。糖尿病控制不佳增加胎兒發生重大先天性缺陷、死胎及巨嬰症相關發病率的風險。

試驗資料

動物試驗資料

在胚胎–胎兒發育試驗中，相當於人類器官形成的第一孕期之懷孕大鼠和兔子施用saxagliptin。依據AUC，大鼠和兔子的暴露量分別達到臨床劑量 5 mg 的 1503 和 152 倍時，兩個物種均未顯示不良發育影響。

對懷孕的大鼠投藥後，saxagliptin 會經由胎盤進入胎兒體內。

在產前及產後發育試驗中，雌性大鼠從妊娠第 6 天到哺乳第 21 天施用 saxagliptin，暴露量依據 AUC 計算，達到臨床劑量 5 mg 的 470 倍時，並未發現不良發育影響。

8.2 哺乳

風險摘要

尚無資料顯示 ONGLYZA 是否會排入人類的乳汁、對接受哺乳嬰兒的影響，或對母乳分泌的作用。

Saxagliptin 會分泌至哺乳大鼠的乳汁中 [見*試驗資料*]。考量哺乳對於發育和健康時，應顧及母親的 ONGLYZA 臨床需求，以及 ONGLYZA 或潛在母體狀況是否對哺乳嬰兒有不良作用。

試驗資料

哺乳中的大鼠，Saxagliptin 會分泌至乳汁中，與血漿藥物濃度的比例約為 1 : 1。

8.3 兒童之使用

尚未確立 ONGLYZA 用於未滿 18 歲的兒童病人的安全性及療效。此外，未有試驗描述 ONGLYZA 在兒童病人之藥動學特性。

8.4 老年人之使用

7 項雙盲且具對照組設計的 ONGLYZA 臨床安全性及功效試驗中，11301 名參與隨機分組的病人中，65 歲以上有 4751 (42.0 %) 人，而 75 歲以上有 1210 (10.7 %) 人。65 歲以上受試者與較年輕的受試者群之間，並未觀察到整體安全性或功效方面的差異。雖然這種臨床經驗在老年人與較年輕病人之間並未發現反應的差別，仍不能排除有些老年人會較為敏感。

Saxagliptin 及其活性代謝產物部分經由腎臟排除。由於老年病人較常有腎功能減退，因此用於老年病人時，應審慎根據腎功能選擇劑量。[參見*用法用量 (2.2) 及臨床藥理學 (12.3)*]

8.6 腎功能不全

在一項為期 12 週的隨機安慰劑對照試驗中，對 85 名有中度 (n=48) 或重度 (n=18) 腎功能不全或末期腎病 (ESRD) (n=19) 的受試者投予 ONGLYZA 2.5mg [參見*臨床研究 (14)*]。ONGLYZA 組和安慰劑的不良事件發生率 (包括嚴重不良事件和因不良事件而停藥) 相似。通報低血糖的總發生率在 ONGLYZA 2.5 mg 治療組是 20 %，安慰劑組是 22 %。有 4 名 ONGLYZA 治療組受試者 (4.7 %) 和 3 名安慰劑組受試者 (3.5 %) 通報至少發生一次經證實的低血糖症狀 (伴有指尖血糖值 ≤ 50 mg/dL)。

10 藥物過量

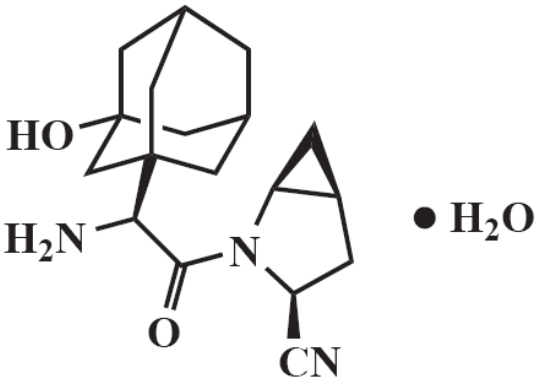
在一項以健康受試者為對象，每日一劑、劑量達 400 mg (80 倍 MRHD)，連續口服 2 週 ONGLYZA 的對照臨床試驗中，並未觀察到劑量相關的臨床不良反應，未伴隨有臨床意義的 QTc 間期或心搏率效應。

如果發生服藥過量，應依病人的臨床狀態給予適當的支持性治療。Saxagliptin 及其活性代謝產物可經由血液透析排出 (4 小時可除去 23 % 的劑量)。

11 說明

Saxagliptin 是 DPP4 酵素的口服活性抑制劑。

Saxagliptin monohydrate 化學名為 (1*S* ,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate or (1*S*,3*S*,5*S*) -2-[(2*S*)-2-Amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrate。實驗式為 $C_{18}H_{25}N_3O_2 \cdot H_2O$，分子量 333.43。結構式如下：



Saxagliptin 單水游離基是白色至淡黃色或淡棕色不吸濕結晶性粉末。在 24°C ± 3°C 時略溶於水，微溶於乙酸乙酯，溶於甲醇、乙醇、異丙醇、乙腈、丙酮及聚乙二醇 400 (PEG 400)。

每顆 ONGLYZA 口服膜衣錠，含有相當於 2.5 mg saxagliptin 的 2.79 mg saxagliptin hydrochloride (無水化合物) 或相當於 5 mg saxagliptin 的 5.58 mg saxagliptin hydrochloride (無水化合物)，以及下列非活性成份：單水乳糖、微晶性纖維素、交聯甲基纖維素鈉和硬脂酸鎂。此外，膜衣錠還含有下列非活性成分：聚乙烯醇、聚乙二醇、二氧化鈦、滑石及氧化鐵。

12 臨床藥理學

12.1 作用機制

進食後小腸會分泌腸泌素如類升糖素胜肽-1 (GLP-1)，以及葡萄糖依賴型胰島素刺激多肽 (GIP)，進入血液。這些荷爾蒙會使胰臟 β 細胞，依葡萄糖濃度高低，釋出胰島素，但在 DPP4 的作用之下，幾分鐘內即失去活性。GLP-1 也會使胰臟 α 細胞的升糖素分泌減少，進而減少肝醣製造。第二型糖尿病病人的 GLP-1 濃度減低，但仍然保有刺激胰島素分泌的功能。Saxagliptin 是一種競爭性的 DPP4 抑制劑，在第二型糖尿病病人體中使腸泌素失去活性的速度減緩，從而增加在血液中的濃度，能依葡萄糖濃度不同而降低空腹及餐後血糖。

12.2 藥效學

在第二型糖尿病病人，投予 ONGLYZA 能夠抑制 DPP4 酵素的活性達 24 小時。口服葡萄糖或進食後，這種 DPP4 抑制作用導致血液循環中活性 GLP-1 及 GIP 的濃度增加 2-3 倍，升糖素濃度降低，葡萄糖依賴性胰島素從胰臟分泌增加。胰島素增加、升糖素減少，與空腹血糖濃度減低。與口服葡萄糖負荷劑量或用餐之後葡萄糖濃度變動減少有關。

心臟電生理學

在一項隨機、雙盲、安慰劑對照、四路交叉的活性對照品試驗中，ONGLYZA 在高達 40 mg 的每日劑量下 (MRHD 的 8 倍) 未伴隨有臨床意義的 QTc 間期或心搏率延長。

12.3 藥動學

Saxagliptin 及活性代謝產物 (5-hydroxy saxagliptin) 的藥動學在健康受試者與第二型糖尿病病人中是類似的。Saxagliptin 及其主要代謝產物的 C_{max} 和 AUC，隨 saxagliptin 劑量增加而成比例增加。對健康的受試者投予 saxagliptin 5 mg 口服劑量後，saxagliptin 及其活性代謝產物的平均血漿 AUC 值各為 78 ng•h/mL 及 214 ng•h/mL；血漿 C_{max} 值各為 24 ng/mL 及 47 ng/mL。Saxagliptin 及其活性代謝物的 AUC 與 C_{max} 的平均變異性 (%CV) 小於 25 %。

以任何劑量每天服用一次重覆給藥後，saxagliptin 及其活性代謝產物都未有蓄積現象。以 2.5 mg 至 400 mg 每天一次的劑量投予 14 天，saxagliptin 及其活性代謝產物的清除率沒有劑量依賴性，亦無時間依賴性。

吸收

每日投予 5 mg saxagliptin，投藥後達最高濃度所需時間的中位數 (T_{max}) 為 2 小時，活性代謝物則在 4 小時達到最高濃度。與空腹投藥相較，於高脂肪飲食後投藥，會使 saxagliptin 的 T_{max} 延長約 20 分鐘。一般餐後服用與空腹投藥相較，saxagliptin 的 AUC 增加 27 %。因此，ONGLYZA 可與食物併服，亦可空腹服用。

分佈

Saxagliptin 及其活性代謝產物在*體外*人類血清中的蛋白質結合可以忽略。因此，預料各種疾病狀態 (如腎或肝功能不全) 血中蛋白質含量的變化不會改變 saxagliptin 的分佈及排除。

代謝

Saxagliptin 主要經由細胞色素 P450 3A4/5 (CYP3A4/5) 代謝。Saxagliptin 的主要代謝產物也是 DPP4 抑制劑，其效價是 saxagliptin 的一半。因此，強效的 CYP3A4/5 抑制劑和誘發物，將改變 saxagliptin 及其活性代謝物的藥動學。[參見*藥物交互作用 (7.1)*]

排泄

Saxagliptin 經由腎臟排泄與肝臟代謝。投予 ^{14}C-saxagliptin 50 mg 的單一劑量後，分別有 24 %、36 % 及 75 % 的劑量以 saxagliptin、其活性代謝產物及總放射活度 (radioactivity) 的形式從尿液排除。Saxagliptin 的平均腎臟清除率 (~230 mL/min) 大於平均估計腎絲球過濾率 (~120 mL/min)，代表有一些腎臟主動分泌作用。所投予的放射性藥物，總計 22 % 從糞便回收，代表由膽汁排除和 / 或未被腸胃道吸收藥物的 saxagliptin 劑量分率。對健康的受試者投予 ONGLYZA 5 mg 的口服劑量之後，saxagliptin 及其主要代謝產物的平均末相半衰期 ($t_{1/2}$) 各為 2.5 小時及 3.1 小時。

特定族群

腎功能不全

使用一項單一劑量開放性試驗，評估 saxagliptin (10 mg 劑量) 用在有各種程度慢性腎功能不全的受試者及腎功能正常者時，藥動學情形如何。10 mg 的劑量不是核准劑量。

腎功能不全的程度，不影響 saxagliptin 或其代謝產物的 C_{max}。對於有中度腎功能不全(eGFR 30 至未達45 mL/min/1.73m^2)、重度腎功能不全 (eGFR 15至未達30 mL/min/1.73 m^2) 和需要接受血液透析的末期腎病病人，saxagliptin或其代謝產物的 AUC 值比腎功能正常者高出2倍。

肝功能不全

對於有肝功能不全的病人 (Child-Pugh 分類 A、B、C 類)，投予 saxagliptin 10 mg 單一劑量後，saxagliptin 的平均 C_{max} 和 AUC 值分別比相對的健康對照組最多高出 8 % 和 77 %。10 mg 的劑量不是核准劑量。活性代謝產物對應的 C_{max} 和 AUC 值分別比相配的健康對照組低 59 % 和 33 %。這些差別並沒有臨床意義。

身體質量指數

不建議根據身體質量指數 (BMI) 調整劑量，在群體藥物動力學分析中，並不將 BMI 並非為 saxagliptin 及其活性代謝產物的擬似清除率的顯著共變數。

性別

不建議根據性別調整劑量。Saxagliptin 的藥動學並無性別差異。相較於男性，女性的活性代謝產物暴露量高出 25 %，但這種差異不太可能有臨床相關性。在群體藥物動力學分析中，性別並非為 saxagliptin 及其活性代謝產物的擬似清除率的顯著共變數。

老年人

不建議單獨根據年齡調整劑量。老年受試者 (65 - 80 歲) saxagliptin 的幾何平均 Cmax 和幾何平均 AUC 值分別比年輕受試者 (18 - 40 歲) 高出 23 % 和 59 %。在老年與年輕受試者之間，活性代謝產物的藥動學差異通常反映在所觀察到的 saxagliptin 藥動學差異上。在年輕與年老的受試者之間，saxagliptin 及其活性代謝產物的藥動學差異可能有多種因素，包括腎功能及代謝能力隨著年紀老邁而減退。在群體藥物動力學分析中，年齡並非為 saxagliptin 及其活性代謝產物的擬似清除率的顯著共變數。

種族與族群

不建議根據種族調整劑量。曾有一項群體藥物動力學分析，比較 saxagliptin 及其主要代謝產物在 309 名白人和 105 名非白人 (由六個種族群體組成) 中的藥動學。在這兩個群體之間，並未偵測到 saxagliptin 及其活性代謝產物的藥動學有顯著差異。

藥物間交互作用研究

藥物交互作用的體外評估

Saxagliptin 主要經由 CYP3A4/5 代謝。

在*體外*試驗，saxagliptin 及其活性代謝產物不會抑制 CYP1A2、2A6、2B6、2C9、2C19、2D6、2E1 或 3A4，也不會誘導 CYP1A2、2B6、2C9 或 3A4。因此，預料 saxagliptin 不會改變經由這些酵素代謝之併服藥物的代謝性清除率。Saxagliptin 為 P-醣蛋白 (P-gp) 的受質，但並非 P-gp 的重要抑制劑或誘導劑。

藥物交互作用的體內評估

表 3：併服藥物對Saxagliptin和 5-hydroxy Saxagliptin 全身暴露量的影響

併服藥物	併服藥物 劑量*	Saxagliptin 劑量*	幾何平均比率 (有／無併服藥物的比率) 無影響 = 1.00		
				AUC†	Cmax
以下無須調整劑量：					
Metformin	1000 mg	100 mg	saxagliptin 5-hydroxy saxagliptin	0.98 0.99	0.79 0.88
Glyburide	5 mg	10 mg	saxagliptin 5-hydroxy saxagliptin	0.98 ND	1.08 ND
Dapagliflozin	單一劑量 10 mg	單一劑量 5mg	saxagliptin 5-hydroxy saxagliptin	↓1% ↑9%	↓7% ↑6%
Pioglitazone‡	45 mg QD 服用 10 天	10 mg QD 服用 5 天	saxagliptin 5-hydroxy saxagliptin	1.11 ND	1.11 ND

併服藥物	併服藥物 劑量*	Saxagliptin 劑量*	幾何平均比率 (有／無併服藥物的比率) 無影響 = 1.00		
				AUC†	C_{max}
Digoxin	第一天 0.25 mg q6h，第二天 q12h，隨後 QD 服用 5 天	10 mg QD 服用 7 天	saxagliptin 5-hydroxy saxagliptin	1.05 1.06	0.99 1.02
Simvastatin	40 mg QD 服用 8 天	10 mg QD 服用 4 天	saxagliptin 5-hydroxy saxagliptin	1.12 1.02	1.21 1.08
Diltiazem	360 mg LA QD 服用 9 天	10 mg	saxagliptin 5-hydroxy saxagliptin	2.09 0.66	1.63 0.57
Rifampin§	600 mg QD 服用 6 天	5 mg	saxagliptin 5-hydroxy saxagliptin	0.24 1.03	0.47 1.39
Omeprazole	40 mg QD 服用 5 天	10 mg	saxagliptin 5-hydroxy saxagliptin	1.13 ND	0.98 ND
Aluminum hydroxide + magnesium hydroxide + simethicone	aluminum hydroxide: 2400 mg magnesium hydroxide: 2400 mg simethicone: 240 mg	10 mg	saxagliptin 5-hydroxy saxagliptin	0.97 ND	0.74 ND
Famotidine	40 mg	10 mg	saxagliptin 5-hydroxy saxagliptin	1.03 ND	1.14 ND
與強效 CYP3A4/5 抑制劑併服時，ONGLYZA 劑量限制在 2.5 mg/1000 mg 每日一次*[參見藥物交互作用(7.1)和用法用量(2.3)]*：					
Ketoconazole	200 mg BID 服用 9 天	100 mg	saxagliptin 5-hydroxy saxagliptin	2.45 0.12	1.62 0.05
Ketoconazole	200 mg BID 服用 7 天	20 mg	saxagliptin 5-hydroxy saxagliptin	3.67 ND	2.44 ND

* 單一劑量，除非另有說明，Saxagliptin 10 毫克不是核准劑量

† 就投予單一劑量的藥物而言，AUC = AUC(INF)，就投予多劑量的藥物而言，AUC = AUC(TAU)

‡ 結果排除一名受試者

§ 在 24 小時的給藥間隔期間，對血漿中 dipeptidyl peptidase-4 (DPP4) 活性的抑制作用不受 rifampin 之影響

ND=未測定；QD=每日一次；q6h=6 小時一次；q12h=12 小時一次；BID=每日二次；LA=長效

表 4：Saxagliptin 對併服藥物全身暴露量的影響

併服藥物	併服藥物 劑量*	Saxagliptin 劑量*	幾何平均比率 (有／無併服藥物的比率) 無影響 = 1.00		
				AUC†	C_{max}
以下無須調整劑量：					
Metformin	1000 mg	100 mg	metformin	1.20	1.09
Glyburide	5 mg	10 mg	glyburide	1.06	1.16
Pioglitazone‡	45 mg QD 服用 10 天	10 mg QD 服用 5 天	pioglitazone hydroxy-pioglitazone	1.08 ND	1.14 ND
Digoxin	第一天 0.25 mg q6h，第二天 q12h，隨後 QD 服用 5 天	10 mg QD 服用 7 天	digoxin	1.06	1.09
Simvastatin	40 mg QD 服用 8 天	10 mg QD 服用 4 天	simvastatin simvastatin acid	1.04 1.16	0.88 1.00
Diltiazem	360 mg LA QD 服用 9 天	10 mg	diltiazem	1.10	1.16
Ketoconazole	200 mg BID 服用 9 天	100 mg	ketoconazole	0.87	0.84
Ethinyl estradiol	ethinyl estradiol 0.035 mg 及	5 mg QD 服用 21 天	ethinyl estradiol	1.07	0.98

併服藥物	併服藥物 劑量*	Saxagliptin 劑量*	幾何平均比率 (有／無併服藥物的比率) 無影響 = 1.00		
				AUC†	C_{max}
及 Norgestimate	norgestimate 0.250 mg 服用 21 天		norelgestromin norgestrel	1.10 1.13	1.09 1.17

* 單一劑量，除非另有說明，Saxagliptin 10 毫克不是核准劑量
† 就投予單一劑量的藥物而言，AUC = AUC(INF)，就投予多劑量的藥物而言，AUC = AUC(TAU)
‡ 結果包括所有受試者
ND=未測定；QD=每日一次；q6h=6 小時一次；q12h=12 小時一次；BID=每日二次；LA=長效

13 非臨床毒理學

13.1 致癌性、致突變性與生殖力損害

致癌性

已於 CD-1 小鼠和 Sprague-Dawley 大鼠進行 2 年期試驗以評估致癌作用。在小鼠口服劑量為 50、250、600 mg/kg，依據AUC，最多達到臨床劑量 5 mg/天的 870 倍 (雄鼠) 及 1165 倍 (雌鼠) 時，saxagliptin 並未增加腫瘤發生率。在大鼠口服劑量為 25、75、150、300 mg/kg，依據 AUC，最多達到臨床劑量 5 mg/天的 355倍 (雄鼠) 及 2217 倍 (雌鼠)，saxagliptin 並未增加腫瘤發生率。

致突變性

在一系列基因毒性檢測 (Ames 細菌致突變性、人類和大鼠淋巴球的細胞遺傳學、大鼠骨髓微核分析及DNA修復分析) 中，並未發現 Saxagliptin (無論活化與否) 會誘發突變。Saxagliptin的活性代謝產物在 Ames 細菌分析中沒有致突變性。

生殖力損害

依據 AUC，雄性和雌性的暴露量最多達到臨床劑量 5 mg 的 603 倍和 776 倍時，施用 saxagliptin 對於大鼠的生育能力或維持胎兒的能力沒有影響。

13.2 動物毒理學和/或藥理學

Saxagliptin 會使長尾彌猴的四肢出現不良的皮膚變化 (尾部、指端、陰囊及／或鼻子的疥癬及／或潰瘍)。在暴露量約為臨床劑量 5 mg的 20 倍範圍內，皮膚傷口均尚為可逆，但在某些情況，於更高暴露劑量下則會不可回復且造成潰爛。暴露於相近於 (1 至 3 倍) 臨床劑量 5 mg ，則未觀察到皮膚變化。在 saxagliptin 的人體臨床試驗中，並未見到與猴子皮膚病灶有臨床相關的情形。

14 臨床試驗

14.1 降血糖療效試驗

以 ONGLYZA 做為單一療法，以及合併 metformin、glyburide、thiazolidinediones 類藥如 pioglitazone、rosiglitazone 進行試驗。

共有 4148 名第二型糖尿病病人經隨機分配，參與 6 項雙盲且具對照組設計的 ONGLYZA 臨床安全性及血糖功效試驗。在這些試驗中，總計有 3021 位病人接受 ONGLYZA 治療。這些試驗對象的平均年齡是 54 歲，71％ 的病人是白人，16％ 是亞洲人，4％ 是黑人，9％ 是其

他種族。另有 423 名病人，包括 315 名接受 ONGLYZA 者，參加一項為期 6 至 12 週的安慰劑對照、劑量範圍試驗。

這六項雙盲試驗評估 2.5 mg 及 5 mg 每天一次劑量的 ONGLYZA。其中三項試驗也評估 ONGLYZA 每天一次 10 mg 的劑量。總體而論，ONGLYZA 10 mg 每天一次的療效不大於 5 mg 每天一次的療效。10 mg 的劑量不是核准劑量。相較於對照組，ONGLYZA 5 mg 及 2.5 mg 劑量組在血紅素 A1c (A1C)、空腹血糖 (FPG)、標準口服葡萄糖耐受性試驗 (OGTT) 後 2 小時的餐後血糖 (PPG)，都有臨床相關性及統計意義的改善。在所有的子群 (包括性別、年齡、種族及 BMI 基準值) 都觀察到 A1C 降低。

相較於安慰劑，ONGLYZA 與體重及空腹血脂的變化無顯著相關。

另外五個以第二型糖尿病病人為對象的臨床試驗也評估過 ONGLYZA：在 858 名單獨使用 metformin 控制不佳的病人中，比較附加 ONGLYZA 和附加 glipizide 療法的活性藥物對照試驗，在 455 名單獨使用胰島素或併用胰島素和metformin控制不佳的病人中，比較 ONGLYZA 和安慰劑的試驗，在 257 名併用metformin和sulfonylurea控制不佳的病人中，比較 ONGLYZA 和安慰劑的試驗，在 315 名併用dapagliflozin和metformin控制不佳的病人中，比較ONGLYZA 和安慰劑的試驗，以及在 170 名有中度或重度腎功能不全或末期腎病 (ESRD) 的第二型糖尿病病人中，比較ONGLYZA 和安慰劑的試驗。

單一療法

共有 766 名以飲食及運動無法充份控制病情的第二型糖尿病病人 (A1C ≥ 7% 至 ≤ 10%)，參與 2 項為期 24 週，雙盲且具安慰劑對照設計的試驗，評估 ONGLYZA 單一用藥的功效與安全性。

在第一項試驗中，經過兩週的單盲飲食、運動及安慰劑導入期之後，401 名病人隨機分配於 ONGLYZA 2.5 mg、5 mg、10 mg 或安慰劑組。10mg的劑量不是核准劑量。試驗期間未達到指定血糖目標的病人，以 metformin 救援療法，附加於安慰劑或 ONGLYZA 治療。對於需要救援治療之病人，療效評估是根據救援前的最後一次數據。ONGLYZA 劑量不得調整。

相較於安慰劑組，ONGLYZA 2.5 mg 及 5 mg 每天一次的治療對 A1C、FPG 及 PPG 均有顯著改善 (表 5)。因血糖控制不良而停止治療，或因符合預定血糖標準而使用救援治療的病人，在 ONGLYZA 2.5 mg 治療組為 16%，ONGLYZA 5 mg 組 20 %，安慰劑組 26 %。

表 5：第二型糖尿病 ONGLYZA 單一療法安慰劑對照試驗第 24 週的血糖數據*

療效指標	**ONGLYZA 2.5 mg N=102**	**ONGLYZA 5 mg N=106**	**安慰劑 N=95**
血紅素 A1C (%)	**N=100**	**N=103**	**N=92**
基準值（平均）	7.9	8.0	7.9
相較於基準值的變化（校正後平均值†）	-0.4	-0.5	+0.2
與安慰劑的差異（校正後平均值†）	-0.6‡	-0.6‡	
95% 信賴區間	(-0.9, -0.3)	(-0.9, -0.4)	
達到 A1C<7% 的病人百分比	35% (35/100)	38%§ (39/103)	24% (22/92)
空腹血漿葡萄糖 (mg/dL)	**N=101**	**N=105**	**N=92**
基準值（平均）	178	171	172
相較於基準值的變化（校正後平均值†）	-15	-9	+6
與安慰劑的差異（校正後平均值†）	-21§	-15§	
95% 信賴區間	(-31, -10)	(-25, -4)	
2 小時餐後血糖 (mg/dL)	**N=78**	**N=84**	**N=71**
基準值（平均）	279	278	283

相較於基準值的變化（校正後平均值†）	-45	-43	-6
與安慰劑的差異（校正後平均值†）	-39¶	-37§	
95% 信賴區間	(-61, -16)	(-59, -15)	

* 意圖治療(ITT)族群，採用試驗中最後一次觀察數據，或需要 metformin 救援治療前最後一次觀察數據。

† 以基準值校正後的最小均方。

‡ 相較於安慰劑，$p < 0.0001$

§ 相較於安慰劑，$p < 0.05$

¶ ONGLYZA 2.5 mg 治療組 2 小時 PPG 並未檢定顯著水準。

第二項為期 24 週的單一療法試驗，評估一系列的 ONGLYZA 用量。未曾接受治療、血糖控制不良 (A1C ≥ 7% 至 ≤ 10 %) 的第二型糖尿病病人，經過兩週的單盲飲食、運動及安慰劑導入期。總計 365 名病人隨機分配，接受 ONGLYZA 2.5 mg 每天早上一次、5 mg 每天早上一次、2.5 mg 可調高到 5 mg 每天早上一次、5 mg 每天晚上一次，或安慰劑治療。

在試驗期間未達到指定血糖目標的病人，以 metformin 救援療法，附加於安慰劑或 ONGLYZA 治療。各治療組隨機分配的病人人數，為 71 至 74 人。

相較於安慰劑，ONGLYZA 5 mg 每天早上一次或 5 mg 每天晚上一次治療，可使 A1C 顯著改善 (安慰劑校正後平均降幅各為 -0.4 % 及 -0.3 %)。相較於安慰劑，ONGLYZA 2.5 mg 每天早上一次治療，A1C 也同樣顯著改善 (安慰劑校正後平均降幅 -0.4 %)。

合併療法

併用 Metformin 的附加合併療法

總計 743 名第二型糖尿病病人參與為期 24 週的隨機、雙盲、安慰劑對照試驗，針對 metformin 單一療法血糖控制不佳的病人 (A1C ≥ 7 % 至 ≤ 10 %)，評估併用 ONGLYZA 與 metformin 的療效與安全性。病人須接受穩定的 metformin 劑量 (每天 1500 mg 至 2550 mg) 至少 8 週，才能參與本試驗。

合格的病人進入單盲、為期 2 週的飲食與運動安慰劑導入期，接受試驗前所服用的 metformin 劑量，最多每天 2500 mg。在導入期之後，合格的病人經隨機分配，除了繼續接受當時服用的開放標記 metformin 劑量之外，再併用 ONGLYZA 2.5 mg、5 mg、10 mg 或安慰劑。10mg的劑量不是核准劑量。試驗期間未達到指定血糖目標的病人，以 pioglitazone 救援療法，附加於安慰劑或 ONGLYZA 治療。ONGLYZA 及 metformin 劑量不得調整。

相較於安慰劑併用 metformin 組，ONGLYZA 2.5 mg 及 5 mg 與 metformin 合併時，A1C、FPG 及 PPG 均得到顯著的改善 (表 6)。各時間點及試驗終點的 A1C 與基準值之間的差異，則如圖 1 所示。因血糖控制不良而停止治療，或因符合預定血糖標準而使用救援治療的病人，在 ONGLYZA 2.5 mg 併用 metformin 組為 15%，ONGLYZA 5 mg 併用 metformin 組為 13%，安慰劑併用 metformin 組為 27%。

表 6：以 ONGLYZA 附加於 Metformin 合併治療、安慰劑對照試驗第 24 週的血糖數據*

療效指標	**ONGLYZA 2.5 mg + Metformin N=192**	**ONGLYZA 5 mg + Metformin N=191**	**安慰劑 + Metformin N=179**
血紅素 A1C (%)	**N=186**	**N=186**	**N=175**
基準值（平均）	8.1	8.1	8.1
相較於基準值的變化（校正後平均值†）	-0.6	-0.7	+0.1
與安慰劑的差異（校正後平均值†）	-0.7‡	-0.8‡	

95% 信賴區間	(-0.9, -0.5)	(-1.0, -0.6)	
達到 A1C<7% 的病人百分比	37%§ (69/186)	44%§ (81/186)	17% (29/175)
空腹血漿葡萄糖 (mg/dL)	**N=188**	**N=187**	**N=176**
基準值（平均）	174	179	175
相較於基準值的變化（校正後平均值†）	-14	-22	+1
與安慰劑的差異（校正後平均值†）	-16§	-23§	
95% 信賴區間	(-23, -9)	(-30, -16)	
2 小時餐後血糖 (mg/dL)	**N=155**	**N=155**	**N=135**
基準值（平均）	294	296	295
相較於基準值的變化（校正後平均值†）	-62	-58	-18
與安慰劑的差異（校正後平均值†）	-44§	-40§	
95% 信賴區間	(-60, -27)	(-56, -24)	

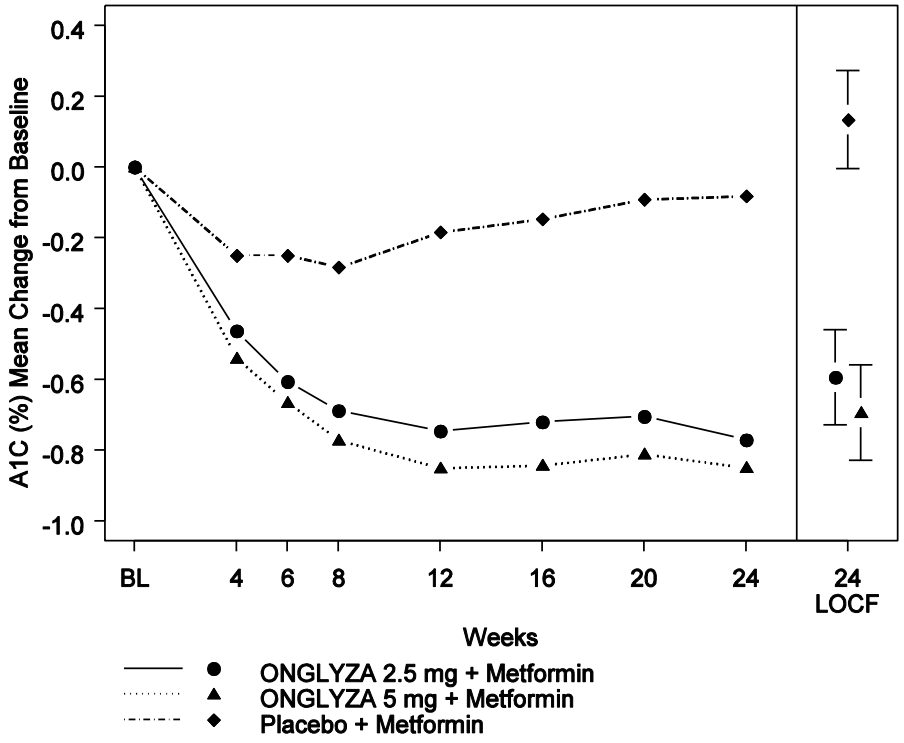
* 意圖治療族群，採用試驗中最後一次觀察數據，或需要 pioglitazone 救援治療前最後一次觀察數據。

† 以基準值校正後的最小均方。

‡ 相較於安慰劑 + metformin，$p < 0.0001$

§ 相較於安慰劑 + metformin，$p < 0.05$

圖 1： 以 ONGLYZA 附加於 Metformin 合併治療、安慰劑對照試驗中 A1C 相較於基準值的變化*



* 包括同時具有基準期及第 24 週觀察值的病人值。

第 24 週 (LOCF) 包括最後一次試驗觀察或需 pioglitazone 救援治療之前最後一次觀察的意圖治療群體。相較於基準值的變化以基準值加以校正。

併用 Thiazolidinedione 的附加合併療法

總計 565 名第二型糖尿病病人參加此項為期 24 週的隨機、雙盲、安慰劑對照試驗，評估 ONGLYZA 與 thiazolidinedione (TZD) 合併用於單獨使用 TZD 血糖控制效果不良病人 (A1C ≥ 7 %至 ≤ 10.5 %) 的療效與安全性。病人必須接受穩定劑量的 pioglitazone (每日 30 - 45 mg)

或 rosiglitazone (4 mg 每天一次，或 8 mg 每天一次或分二次服用，每次 4 mg) 至少 12 週才能進入此項研究。

達到合格標準的病人進入單盲、為期 2 週的飲食與運動安慰劑導入期，接受其進入試驗以前的 TZD 劑量。在導入期之後，合格的病人除了繼續服用當時的開放性 TZD 劑量之外，並經隨機分配併用 ONGLYZA 2.5 mg 或 5 mg、或安慰劑。試驗期間未達到達成指定血糖目標的病人，用 metformin 救援療法，附加於安慰劑或 ONGLYZA 之上治療。ONGLYZA 及 TZD 劑量不得調整。倘若認為在醫療上適當，試驗主持人可自行決定，使用明定相當的治療劑量，將 TZD 療法由 rosiglitazone 改為 pioglitazone。

相較於安慰劑加TZD組，ONGLYZA 2.5 mg 及 5 mg 與TZD合併時，A1C、FPG 及 PPG 均得到顯著的改善 (表 7)。因血糖控制不良而停止治療，或因符合預定血糖標準而使用救援治療的病人，在 ONGLYZA 2.5 mg 併用 TZD 組為 10%，ONGLYZA 5 mg 併用 TZD 組為 6%，安慰劑併用 TZD 組為 10%。

表 7： 以 ONGLYZA 附加於 Thiazolidinedione 合併治療、安慰劑對照試驗第 24 週的血糖數據*

療效指標	**ONGLYZA 2.5 mg + TZD N=195**	**ONGLYZA 5 mg + TZD N=186**	**安慰劑 + TZD N=184**
血紅素 A1C (%)	**N=192**	**N=183**	**N=180**
基準值（平均）	8.3	8.4	8.2
相較於基準值的變化（校正後平均值†）	-0.7	-0.9	-0.3
與安慰劑的差異（校正後平均值†）	-0.4§	-0.6‡	
95% 信賴區間	(-0.6, -0.2)	(-0.8, -0.4)	
達到 A1C<7% 的病人百分比	42%§ (81/192)	42%§ (77/184)	26% (46/180)
空腹血漿葡萄糖 (mg/dL)	**N=193**	**N=185**	**N=181**
基準值（平均）	163	160	162
相較於基準值的變化（校正後平均值†）	-14	-17	-3
與安慰劑的差異（校正後平均值†）	-12§	-15§	
95% 信賴區間	(-20, -3)	(-23, -6)	
2 小時餐後血糖 (mg/dL)	**N=156**	**N=134**	**N=127**
基準值（平均）	296	303	291
相較於基準值的變化（校正後平均值†）	-55	-65	-15
與安慰劑的差異（校正後平均值†）	-40§	-50§	
95% 信賴區間	(-56, -24)	(-66, -34)	

* 意圖治療(ITT)族群，採用試驗中最後一次觀察數據，或需要 metformin 救援治療前最後一次觀察數據。

† 以基準值校正後的最小均方。

‡ 相較於安慰劑 + TZD，$p < 0.0001$

§ 相較於安慰劑 + TZD，$p < 0.05$

併用 Glyburide 的附加合併療法

總計 768 名第二型糖尿病病人參加此項為期 24 週的隨機、雙盲、安慰劑對照試驗，評估 ONGLYZA 與磺醯尿素類藥品 (SU) 合併於單獨使用 SU 次大劑量 (submaximal dose) 後血糖控制效果不良病人 (A1C ≥ 7.5 % 至 ≤ 10 %) 的療效與安全性。病人必須接受 SU 的次大劑量至少 2 個月才能進入此項試驗。在此項試驗中，ONGLYZA 與固定中間劑量 SU 的合併療法，與 ONGLYZA 併用可調至更高劑量的SU組進行比較。

達到合格標準的病人進入單盲、為期 4 週的飲食與運動安慰劑導入期，並接受 glyburide 7.5 mg 每天一次。在導入期之後，合格的病人經隨機分配接受 ONGLYZA 2.5 mg 或 5 mg 附加於 glyburide 7.5 mg、或安慰劑併用 glyburide 每天 10 mg。接受安慰劑的病人，glyburide 劑量可以調高到每天 15 mg。接受 ONGLYZA 2.5 或 5 mg 的病人，不可調高 glyburide 劑量。在 24 週試驗期間，只要試驗主持人認為有需要，任一治療組的 glyburide 劑量皆可因低血糖調降一次。安慰劑加 glyburide 組約有 92 % 病人在試驗期間的最初 4 週調高劑量，最後達到 15 mg 的每日總量。試驗期間未達到達成指定血糖目標的病人，用 metformin 救援療法，附加於安慰劑或 ONGLYZA 之上治療。ONGLYZA 劑量不得調整。

相較於安慰劑加調高劑量的 glyburide 組，ONGLYZA 2.5 mg 及 5 mg 與 glyburide 合併時，A1C、FPG 及 PPG 得到顯著的改善 (表 8)。因血糖控制不良而停止治療，或因符合預定血糖標準而使用救援治療的病人，在 ONGLYZA 2.5 mg 併用 glyburide 組為 18 %，ONGLYZA 5 mg 併用 glyburide 組為 17 %，安慰劑併用 glyburide 組為 30 %。

表 8：以 ONGLYZA 附加於 Glyburide 合併治療、安慰劑對照試驗第 24 週的血糖數據*

療效指標	**ONGLYZA 2.5 mg + Glyburide 7.5 mg N=248**	**ONGLYZA 5 mg + Glyburide 7.5 mg N=253**	**安慰劑 + Glyburide 調高劑量 N=267**
血紅素 A1C (%)	**N=246**	**N=250**	**N=264**
基準值（平均）	8.4	8.5	8.4
相較於基準值的變化（校正後平均值†）	-0.5	-0.6	+0.1
與 glyburide 調高劑量的差異（校正後平均值†）	-0.6‡	-0.7‡	
95% 信賴區間	(-0.8, -0.5)	(-0.9, -0.6)	
達到 A1C<7% 的病人百分比	22%§ (55/246)	23%§ (57/250)	9% (24/264)
空腹血漿葡萄糖 (mg/dL)	**N=247**	**N=252**	**N=265**
基準值（平均）	170	175	174
相較於基準值的變化（校正後平均值†）	-7	-10	+1
與 glyburide 調高劑量的差異（校正後平均值†）	-8§	-10§	
95% 信賴區間	(-14, -1)	(-17, -4)	
2 小時餐後血糖 (mg/dL)	**N=195**	**N=202**	**N=206**
基準值（平均）	309	315	323
相較於基準值的變化（校正後平均值†）	-31	-34	+8
與 glyburide 調高劑量的差異（校正後平均值†）	-38§	-42§	
95% 信賴區間	(-50, -27)	(-53, -31)	

* 意圖治療(ITT)族群，採用試驗中最後一次觀察數據，或需要 metformin 救援治療前最後一次觀察數據。

† 以基準值校正後的最小均方。

‡ 相較於安慰劑 + glyburide 調高劑量，$p < 0.0001$

§ 相較於安慰劑 + glyburide 調高劑量，$p < 0.05$

與 Metformin 併用於未曾接受治療的病人

總計 1306 名第二型糖尿病病人參加此項為期 24 週的隨機、雙盲、活性藥物對照試驗，評估 ONGLYZA 與 metformin 合併作為起始治療對於僅以飲食及運動無法適當控制血糖病人 (A1C ≥ 8 % 至 ≤ 12 %) 的療效與安全性。病人必須未曾接受治療才能進入此項試驗。

達到合格標準的病人進入單盲、為期 1 週的飲食與運動安慰劑導入期。病人隨機分成四組：ONGLYZA 5 mg + metformin 500 mg、saxagliptin 10 mg + metformin 500 mg、saxagliptin 10 mg +

安慰劑、或 metformin 500 mg + 安慰劑。saxagliptin 10mg的劑量不是核准劑量。ONGLYZA 每天服用一次。施用 metformin 的三個治療組，每週調高 metformin 劑量，每次提高 500 mg日劑量，在可耐受的情況下，依 FPG 數據，最高調整到每日 2000 mg。試驗期間未達到達成指定血糖目標的病人，以 pioglitazone 作為附加療法治療。

相較於安慰劑 + metformin，併用 ONGLYZA 5 mg 與 metformin 治療時，A1C、FPG 及 PPG 均顯著改善 (表 9)。

表 9： 針對未曾接受治療的病人，以 ONGLYZA 併用 Metformin、安慰劑對照試驗第 24 週的血糖數據*

療效指標	**ONGLYZA 5 mg + Metformin N=320**	**安慰劑 + Metformin N=328**
血紅素 A1C (%)	**N=306**	**N=313**
基準值（平均）	9.4	9.4
相較於基準值的變化（校正後平均值†）	-2.5	-2.0
與安慰劑 + metformin 的差異（校正後平均值†）	-0.5‡	
95% 信賴區間	(-0.7, -0.4)	
達到 A1C<7% 的病人百分比	60%§ (185/307)	41% (129/314)
空腹血漿葡萄糖 (mg/dL)	**N=315**	**N=320**
基準值（平均）	199	199
相較於基準值的變化（校正後平均值†）	-60	-47
與安慰劑 + metformin 的差異（校正後平均值†）	-13§	
95% 信賴區間	(-19, -6)	
2 小時餐後血糖 (mg/dL)	**N=146**	**N=141**
基準值（平均）	340	355
相較於基準值的變化（校正後平均值†）	-138	-97
與安慰劑 + metformin 的差異（校正後平均值†）	-41§	
95% 信賴區間	(-57, -25)	

* 意圖治療(ITT)族群，採用試驗中最後一次觀察數據，或需要 pioglitazone 救援治療前最後一次觀察數據。

† 以基準值校正後的最小均方。

‡ 相較於安慰劑 + metformin，$p < 0.0001$

§ 相較於安慰劑 + metformin，$p < 0.05$

附加於 Metformin 之合併療法和 Glipizide 附加於 Metformin之合併療法的比較

在這個為期 52 週的活性藥物對照試驗中，總計 858 名單獨使用 metformin 控制不佳 (A1C > 6.5 % 且 ≤10 %) 的第二型糖尿病病人隨機分組，接受雙盲 ONGLYZA 或 glipizide 附加療法。進入試驗前，病人必須服用穩定的 metformin 劑量 (至少每天 1500 mg) 至少 8 週。

合格的病人進入單盲、為期 2 週的飲食與運動安慰劑導入期，接受 metformin (根據試驗前所服用的劑量，1500-3000 mg)。在導入期之後，合格的病人經隨機分配，除了繼續接受當時服用的開放標記 metformin 劑量之外，再併用 ONGLYZA 5 mg 或 glipizide。Glipizide 加 metformin 組病人在試驗頭 18 週進行盲性 glipizide 劑量調整，最多至 glipizide 的最高劑量每天 20 mg。劑量調整以 FPG ≤ 110 mg/dL 的目標或 glipizide 的最大耐受劑量為依據。接受 glipizide 治療的病人，有 50 % 的 glipizide 劑量調高到每天 20 mg；21 % 的 glipizide 最終每日劑量是 5 mg 或更低。Gipizide 的最終每日劑量平均是 15 mg。

當 ONGLYZA 與 glipizide 附加於 metformin 療法，治療 52 週之後，兩組的 A1C 從基準值的平均降幅類似 (表10)。這個結論可能限於 A1C 基準值與本試驗相當的病人 (91 % 病人的 A1C 基準值 < 9 %)。

接受 ONGLYZA 治療的病人，體重從 89 公斤的平均基準值平均減輕 1.1 公斤，這在統計上是有意義的，而接受 glipizide 的病人則平均增加 1.1 公斤 (p<0.0001)。

表 10：比較 ONGLYZA 和 Glipizide 分別與 Metformin 併用的活性藥物對照試驗第 52 週的血糖數據*

療效指標	**ONGLYZA 5 mg + Metformin N=428**	**劑量調整的Glipizide + Metformin N=430**
血紅素 A1C (%)	**N=423**	**N=423**
基準值（平均）	7.7	7.6
相較於基準值的變化（校正後平均值†）	-0.6	-0.7
與 glipizide + metformin 的差異（校正後平均值†）	0.1	
95% 信賴區間	(-0.02, -0.2)‡	
空腹血漿葡萄糖 (mg/dL)	**N=420**	**N=420**
基準值（平均）	162	161
相較於基準值的變化（校正後平均值†）	-9	-16
與 glipizide + metformin 的差異（校正後平均值†）	6	
95% 信賴區間	(-2, 11)§	

* 意圖治療(ITT)族群，採用試驗中最後一次觀察數據，或需要 pioglitazone 救援治療前最後一次觀察數據。

† 以基準值校正後的最小均方。

‡ 因為此信賴區間上限小於預定的非劣性邊際值，所以認為 ONGLYZA + metformin 不劣於 glipizide + metformin

§ 未檢定顯著性

併用胰島素的附加合併療法(併用或未併用metformin)

總計 455 名第二型糖尿病病人參加此項為期 24 週的隨機、雙盲、安慰劑對照試驗，評估 ONGLYZA 與胰島素合併使用對於單獨使用胰島素 (N=141) 或併用胰島素和穩定的 metformin 劑量 (N=314) 後血糖控制不良病人 (A1C ≥ 7.5 % 至 ≤ 11%) 的療效與安全性。篩選前，病人必須使用穩定的胰島素劑量 (每天 ≥ 30 單位至 ≤ 150 單位)，每日總量變動 ≤ 20 % 至少 8 週。病人進入試驗接受中效或長效 (基礎) 胰島素或預混型胰島素。使用短效胰島素的病人被排除，除非短效胰島素是作為預混型胰島素的一部分。

達到合格標準的病人進入單盲、為期 4 週的飲食與運動安慰劑導入期，並接受試驗前使用的胰島素劑量 (併用或不併用metformin)。在導入期之後，合格的病人經隨機分配接受 ONGLYZA 5 mg 或安慰劑附加療法。抗糖尿病藥物的劑量保持穩定，如果試驗期間未達到達成指定血糖目標，或者試驗主持人得知病人自行調高胰島素劑量 > 20 %，則給予救援療法並容許調整胰島素的劑量。救援後的數據被排除於主要療效分析之外。

使用ONGLYZA 5 mg 附加療法使第 24 週的 A1C 和 PPG 得到顯著的改善 (表 11)。相較於安慰劑組，ONGLYZA 5 mg 附加於單獨使用胰島素組與ONGLYZA 5 mg 附加於胰島素及 metformin 合併療法組的 A1C 從基準值的平均降幅類似 (分別是−0.4 %和−0.4 %)。因血糖控制不良而停止治療，或使用救援治療的病人百分比，在 ONGLYZA 組為 23 %，安慰劑組為 32 %。

基準期的平均胰島素每日劑量在 ONGLYZA 5 mg 治療組是 53 單位，安慰劑治療組是 55 單位。胰島素每日劑量相較於基準值的變化在 ONGLYZA 5 mg 組是 2 單位，安慰劑治療組是 5 單位。

表 11：以 ONGLYZA 附加於胰島素合併治療的安慰劑對照試驗第 24 週的血糖數據*

療效指標	**ONGLYZA 5 mg + 胰島素 (+/- Metformin) N=304**	**安慰劑 + 胰島素 (+/- Metformin) N=151**
血紅素 A1C (%)	**N=300**	**N=149**
基準值（平均）	8.7	8.7
相較於基準值的變化（校正後平均值†）	−0.7	−0.3
與安慰劑組間的差異（校正後平均值†）	−0.4‡	
95% 信賴區間	(−0.6, −0.2)	
2 小時餐後血糖 (mg/dL)	**N=262**	**N=129**
基準值（平均）	251	255
相較於基準值的變化（校正後平均值†）	−27	−4
與安慰劑組間的差異（校正後平均值†）	−23§	
95% 信賴區間	(−37, −9)	

* 意圖治療(ITT)族群，採用試驗中最後一次觀察數據，或需要胰島素救援治療前最後一次觀察數據。

† 以基準值及基準期使用metformin校正後的最小均方。

‡ 相較於安慰劑+胰島素，$p < 0.0001$

§ 相較於安慰劑+胰島素，$p < 0.05$

也檢測了空腹血糖從基線到 24 週的變化，但無統計學意義。ONGLYZA 與胰島素合併療法組達到 A1C < 7 % 的病人百分比是 17 % (52/300)，安慰劑組是 7 % (10/149)。沒有檢定顯著性。

併用Metformin加Sulfonylurea的附加合併療法

總計 257 名第二型糖尿病病人參加此項為期 24 週的隨機、雙盲、安慰劑對照試驗，評估 ONGLYZA 與 metformin 加 sulfonylurea 合併使用對於血糖控制不良病人 (A1C ≥ 7 % 至 ≤ 10%) 的療效與安全性。進入試驗前，病人必須使用穩定的 metformin 持續釋放型或立即釋放型劑量 (最大耐受劑量，進入試驗的最低劑量是1500mg) 和 sulfonylurea 劑量 (最大耐受劑量，進入試驗的最低劑量 ≧ 50 % 最大建議劑量) 至少 8 週。

達到合格標準的病人進入為期 2 週的參加期，評估納入/排除條件。在參加期之後，合格的病人經隨機分配接受雙盲 ONGLYZA (每天5 mg) 或相配的雙盲安慰劑治療24週。在24週雙盲治療期間，病人接受的 metformin 和 sulfonyurea 劑量與在參加期確定的固定劑量相同。如果發生重大低血糖事件或輕微低血糖事件復發，sulfonylurea 的劑量可以調低一次。若未發生低血糖事件，治療期間不容許調整 (調高或調低) 研究藥物的劑量。

相較於安慰劑與 metformin 加 sulfonyurea 併用，ONGLYZA 與 metformin 加 sulfonyurea 併用使 A1C 和 PPG 得到顯著的改善 (表 12)。因血糖控制不良而停止治療的病人百分比，在 ONGLYZA 組為 6 %，安慰劑組為 5 %。

表 12: 以 ONGLYZA 附加於 Metformin 加 Sulfonylurea 合併治療的安慰劑對照試驗第 24 週的血糖數據*

療效指標	**ONGLYZA 5 mg + Metformin 加 Sulfonylurea N=129**	**安慰劑 + Metformin 加 Sulfonylurea N=128**

表 12: 以 ONGLYZA 附加於 Metformin 加 Sulfonylurea 合併治療的安慰劑對照試驗第 24 週的血糖數據*

療效指標	**ONGLYZA 5 mg + Metformin 加 Sulfonylurea N=129**	**安慰劑 + Metformin 加 Sulfonylurea N=128**
血紅素 A1C (%)	**N=127**	**N=127**
基準值（平均）	8.4	8.2
相較於基準值的變化（校正後平均值†）	−0.7	−0.1
與安慰劑組間的差異（校正後平均值†）	−0.7‡	
95% 信賴區間	(−0.9, −0.5)	
2 小時餐後血糖 (mg/dL)	**N=115**	**N=113**
基準值（平均）	268	262
相較於基準值的變化（校正後平均值†）	−12	5
與安慰劑組間的差異（校正後平均值†）	−17§	
95% 信賴區間	(−32, −2)	

* 意圖治療族群，採用試驗中最後一次觀察數據。

† 以基準值校正後的最小均方。

‡ 相較於安慰劑+ metformin 加 sulfonylurea，$p < 0.0001$

§ 相較於安慰劑+ metformin 加 sulfonylurea，$p < 0.05$

也檢測了空腹血糖從基線到24週的變化，但無統計學意義。ONGLYZA與metformin加sulfonylurea合併療法組達到 A1C <7%的病人百分比是31% (39/127)，安慰劑組是9% (12/127)。沒有檢定顯著性。

與 Metformin 及 SGLT2 抑制劑的附加合併治療

總計 315 名第二型糖尿病病人參加這項為期 24 週的隨機、雙盲、安慰劑對照試驗，針對基準點 HbA1c ≥ 7 % 至 ≤ 10.5 % 的病人，評估 ONGLYZA 附加於 dapagliflozin (一種 SGLT2 抑制劑) 和 metformin 的療效與安全性。這些受試者的平均年齡為 54.6 歲，其中 1.6 % 為 75 歲以上，且 52.7 % 為女性。試驗族群包含白人 87.9 %、黑人或非裔美國人 6.3 %、亞洲人 4.1 % 和其他種族 1.6 %。基準點時試驗族群罹患糖尿病平均 7.7 年，平均 HbA1c 為 7.9 %。基準點平均 eGFR 為 93.4 mL/min/1.73 m^2。參加試驗之前，病人需已接受穩定劑量的 metformin (每天 ≥1500 mg) 至少 8 週。合格受試者完成篩選期後，將開始導入治療期，包括開放標記 metformin 和 10 mg dapagliflozin 治療。導入期之後，合格受試者隨機分配至 ONGLYZA 5 mg (N=153) 或安慰劑 (N =162)。

附加 ONGLYZA 治療組的 HbA1c 自基準點的減幅於統計上顯著地大於安慰劑組 (見表 13)。

表 13：ONGLYZA 附加於 Dapagliflozin 及 Metformin 的安慰劑對照試驗，第 24 週 HbA1c 自基準點的變化§

	ONGLYZA 5 mg (N=153)†	**安慰劑 (N=162)**
	併用 Dapagliflozin 和 Metformin	
血紅素 A1C (%)*		

基準點 (平均)	8.0	7.9
自基準點的變化 (校正後平均值‡) 95% 信賴區間	-0.5 (-0.6, -0.4)	-0.2 (-0.3, -0.1)
與安慰劑的差異 (校正後平均值) 95% 信賴區間	-0.4¶ (-0.5, -0.2)	

* 共變數分析納入所有基準點後資料，不論使用急救藥物或停藥。模型估計值是以多重插補法計算而得，在建模當中，遺失第 24 週資料受試者的安慰劑療效因子均已排除。

† 隨機分配且接受治療的病人數。

‡ 以基準值校正後的最小均方。

§ 於第 24 週時，在隨機分配受試者中，Saxagliptin 組有 6.5% (n=10) 及安慰劑組有 3.1% (n=5) 的受試者缺少自 HbA1c 基準值的數據變化。於提早停止治療的受試者中，在 Saxagliptin 組有 9.1% (11 名中有 1 名) 及在安慰劑組有 16.7% (6 名中有 1 名) 於第 24 週時測量 HbAlc。

¶ p 值 < 0.0001

第 24 週時達到 HbA1c < 7% 的已知病人比例為：saxagliptin 治療組為 35.3%；安慰劑治療組為 23.1%。

14.2 腎功能不全

總計 170 名第二型糖尿病病人參與一項為期 12 週的隨機、雙盲、安慰劑對照試驗，針對有中度 (n=90) 或重度 (n=41) 腎功能不全或末期腎病 (n=39) 的第二型糖尿病病人，評比 ONGLYZA 2.5 mg 每天一次與安慰劑的療效與安全性。在這個試驗中，98% 的病人正在使用抗糖尿病藥物 (75% 使用胰島素，31% 使用口服抗糖尿病藥物，大多是 sulfonylureas)。

治療 12 週之後，相較於安慰劑組，ONGLYZA 2.5 mg 組的 A1C 有顯著的改善 (表14)。在有末期腎病的病人亞群中，ONGLYZA 組和安慰劑組的 A1C 從基準線至第 12 週的降幅相當。這個結果並不確鑿，因為這個試驗的檢力不足以顯示在特定的腎功能不全次群內的療效。

治療 12 週之後，FPG 的平均變化在 ONGLYZA 2.5 mg 組是 -12 mg/dL，安慰劑組是 -13 mg/dL。相較於安慰劑組，ONGLYZA 組 FPG 的平均變化在有中度腎功能不全的病人亞群是 -12 mg/dL，有重度腎功能不全的病人亞群是 -4 mg/dL，有末期腎病 (n=39) 的病人亞群是 +44 mg/dL。這些結果並不確鑿，因為這個試驗的檢力不足以顯示在特定的腎功能不全次群內的療效。

表 14：ONGLYZA 的安慰劑對照試驗中腎功能不全病人第 12 週的 A1C*

療效指標	**ONGLYZA 2.5 mg N=85**	**安慰劑 N=85**
血紅素 A1C (%)	**N=81**	**N=83**
基準值（平均）	8.4	8.1
相較於基準值的變化（校正後平均值†）	-0.9	-0.4
與安慰劑的差異（校正後平均值†）	-0.4‡	
95% 信賴區間	(-0.7, -0.1)	

* 意圖治療族群，採用試驗中最後一次觀察數據。

† 以基準值校正後的最小均方。

‡ 相較於安慰劑，p < 0.01

14.3 心血管安全性試驗

ONGLYZA的心血管風險在SAVOR試驗進行了評估，這是一項多中心、多國、隨機、雙盲研究，

在有高風險罹患動脈粥樣硬化心血管疾病的第二型糖尿病成人病人中，比較 ONGLYZA (N=8280) 和安慰劑 (N =8212)，二者皆合併標準療法。在隨機分配的受試者中，97.5 % 完成了試驗，中位追蹤時間約2年。此為事件驅動試驗 (event-driven trial)，並且追蹤病人直到累積了足夠數量的事件為止。

受試者的年齡至少 40 歲，A1C ≥ 6.5 %，且有多種心血管疾病的危險因子 (男性 ≥ 55 歲和女性 ≥ 60 歲，加上至少另一種危險因子：血脂異常、高血壓、或當時還有吸煙) (佔隨機分配受試者的 21 %)，或已確定有心血管疾病 (佔隨機分配受試者的 79 %)，其定義為有缺血性心臟病、周邊血管疾病或缺血性中風的病史。整體而言，所有治療組的糖尿病藥物使用情形相近 (metformin 69 %、胰島素 41 %、磺醯脲類藥物 40 %、TZD 6 %)。心血管疾病藥物的使用情形也類似 (血管收縮素轉化酶 [ACE] 抑制劑或血管收縮素受體阻斷劑 [ARB] 79%、史塔汀 [statin] 類 78 %、阿斯匹靈 75 %、β 阻斷劑 62 %，及非阿斯匹靈抗血小板藥物 24 %)。

大多數受試者為男性 (67 %) 和高加索人 (75 %)，平均年齡為 65 歲。受試族群中約有 16 % 為中度 (預估腎小球濾過率 [eGFR] ≥ 30至 ≤ 50 mL/min) 至重度 (eGFR < 30 mL/min) 腎功能不全，13 % 有心衰竭病史。受試者的第二型糖尿病中位病程約 10 年，平均A1C基準值為8.0 %。約 5 % 受試者在基準期時只接受飲食和運動治療。總體而言，各治療組糖尿病藥物的使用情形相當 (metformin 69 %，胰島素 41 %，sulfonylurea 40 %，TZD 類 6 %)，心血管疾病藥物的使用情形也相當 (ACE抑制劑或ARB類 79 %，statin類 78 %，aspirin 75 %，β-阻斷劑 62 %，和非 aspirin 抗血小板藥物 24 %)。

在 SAVOR 試驗中，主要分析是第一次出現重大不良心臟事件 (Major Adverse Cardiac Event, MACE) 的時間。在 SAVOR 試驗中，重大不良心臟事件被定義為心血管死亡、非致死性心肌梗塞 (MI)、或非致死性缺血性中風。這項研究的設計是作為非劣性試驗，MACE 風險比的預設風險邊際值為 1.3，如果非劣性被證明，也有檢力比較優效性。

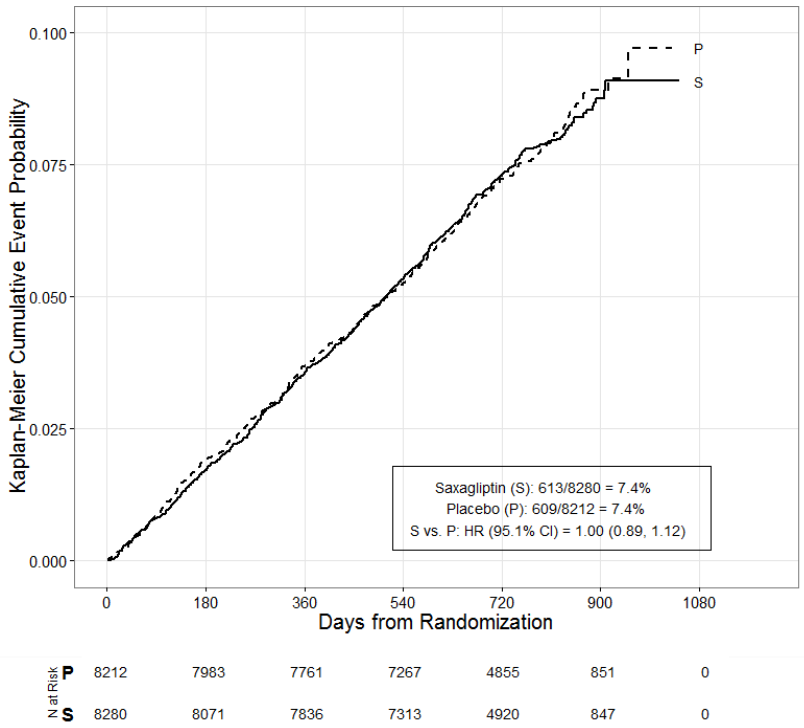
表 15 顯示 SAVOR 試驗的結果，包括單一事件對主要綜合試驗終點的貢獻。兩個治療組的 MACE 發生率相似：安慰劑組每 100 病人-年有 3.8 例 MACE，ONGLYZA 治療組每 100 病人-年有 3.8 例 MACE。Saxagliptin 相對於安慰劑的 MACE 預估風險比為 1.00，95.1 % 信賴區間 (0.89，1.12)。此信賴區間的上限 1.12，排除了大於 1.3 的風險邊際值。

表15：在 SAVOR 試驗中各治療組的重大不良心臟事件 (MACE)

	ONGLYZA		**安慰劑**		**風險比**
	受試者人數 (%)	**每100病人-年發生率**	**受試者人數 (%)**	**每100病人-年發生率**	**(95.1% CI)**
第一次心血管死亡、非致死性心肌梗塞或非致死性缺血性中風事件(MACE)的綜合終點	**N=8280**	**總病人-追蹤年數= 16308.8**	**N=8212**	**總病人-追蹤年數= 16156.0**	
	613 (7.4)	3.8	609 (7.4)	3.8	1.00 (0.89, 1.12)
心血管(CV)死亡	245 (3.0)	1.5	234 (2.8)	1.4	
非致死性心肌梗塞 (MI)	233 (2.8)	1.4	260 (3.2)	1.6	
非致死性缺血性中風	135 (1.6)	0.8	115 (1.4)	0.7	

圖 2 顯示各治療組自隨機分配至第一次出現主要 MACE 綜合試驗終點的累積事件機率 Kaplan-Meier 曲線。ONGLYZA 組和安慰劑組的曲線在整個試驗期間一直靠得很近。兩組的預估累積事件機率都幾乎呈現線性，這顯示兩組的 MACE 發生率在試驗期間保持一致。

圖 2：自隨機分配至第一次出現MACE的累積百分比



本試驗取得了99 % 受試者的存活狀態。在 SAVOR 試驗中，共有 798 人死亡。在數值上，ONGLYZA 組死亡的病人 (5.1 %) 比安慰劑組 (4.6 %) 多。治療組間所有原因死亡的風險 (表 16) 沒有統計上的差異 (HR：1.11；95.1 % CI：0.96，1.27)。

表16：SAVOR 試驗中各治療組的所有原因死亡率

	ONGLYZA		**安慰劑**		**風險比**
	受試者人數 (%)	**每100病人-年發生率**	**受試者人數 (%)**	**每100病人-年發生率**	**(95.1% CI)**
	N=8280	**病人-追蹤年數=16645.3**	**N=8212**	**病人-追蹤年數=16531.5**	
所有原因死亡	420 (5.1)	2.5	378 (4.6)	2.3	1.11 (0.96, 1.27)
心血管死亡	269 (3.2)	1.6	260 (3.2)	1.6	
非心血管死亡	151 (1.8)	0.9	118 (1.4)	0.7	

16 包裝/儲存與處理

包裝

ONGLYZA® (saxagliptin) 錠的兩面皆有標誌，規格與包裝列於表 17。

表 17：ONGLYZA 錠外觀

錠劑含量	膜衣錠 顏色/形狀	錠劑標誌	包裝大小
5 mg	粉紅色	一面標示 “5”	鋁箔

	兩面凸出、圓形	另一面標示 “4215” 藍色字體	
2.5 mg	淺黃至淡黃色 兩面凸出、圓形	一面標示 “2.5” 另一面標示 “4214” 藍色字體	鋁箔

包裝規格

請參閱外包裝上之包裝規格。

儲存與處理

儲存於 30 ºC 以下。

有效期限

標示於藥品鋁箔與外盒上。

製造廠：AstraZeneca Pharmaceuticals LP

廠　址：4601 Highway 62 East, Mount Vernon, Indiana 47620, USA

分裝廠：AstraZeneca UK Limited

廠　址：Silk Road Business Park Macclesfield, Cheshire, SK10 2NA, United Kingdom

藥　商：臺灣阿斯特捷利康股份有限公司

地　址：台北市敦化南路二段207號21樓

修訂日期：2018 年 12 月

Onglyza US PI 2017/02

AstraZeneca

PACKAGE LEAFLET TEXT

Onglyza®

(saxagliptin)

Film-coated tablets 2.5mg, 5mg

1 INDICATIONS AND USAGE

Type 2 diabetes mellitus [See *Clinical Studies (14).*]

1.1 Important Limitations of Use

ONGLYZA is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of ONGLYZA is 2.5 mg or 5 mg once daily as monotherapy or as combination therapy with metformin, a sulfonylurea, a PPARγ agonist (i.e., thiazolidinediones), insulin (with or without metformin), metformin plus a sulfonylurea, or metformin plus dapagliflozin, as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. Onglyza can be taken regardless of meals. [See *Clinical Studies (14).*]

2.2 Dosage in Patients with Renal Impairment

No dosage adjustment for ONGLYZA is recommended for patients with eGFR ≥45mL/min/1.73 m^2.

The dosage of ONGLYZA is 2.5 mg once daily (regardless of meals) for patients with eGFR <45mL/min/1.73 m^2 (which includes a subset of moderate or severe renal impairment, or with end-stage renal disease (ESRD) requiring hemodialysis [see *Clinical Pharmacology (12.3)* and *Clinical Studies (14.2)*]. ONGLYZA should be administered following hemodialysis. ONGLYZA has not been studied in patients undergoing peritoneal dialysis.

Because the dosage of ONGLYZA should be limited to 2.5 mg based upon renal function, assessment of renal function is recommended prior to initiation of ONGLYZA and periodically thereafter.

2.3 Dosage Adjustment with Concomitant Use of Strong CYP3A4/5 Inhibitors

The dosage of ONGLYZA is 2.5 mg once daily when coadministered with strong cytochrome P450 3A4/5 (CYP3A4/5) inhibitors (e.g., ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin). [See *Drug Interactions (7.1)* and *Clinical Pharmacology (12.3).*]

2.4 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

When ONGLYZA is used in combination with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia. [See *Warnings and Precautions (5.3)*.]

3 DOSAGE FORMS AND STRENGTHS

- ONGLYZA (saxagliptin) 5 mg tablets are pink, biconvex, round, film-coated tablets with "5" printed on one side and "4215" printed on the reverse side, in blue ink.
- ONGLYZA (saxagliptin) 2.5 mg tablets are pale yellow to light yellow, biconvex, round, film-coated tablets with "2.5" printed on one side and "4214" printed on the reverse side, in blue ink.

4 CONTRAINDICATIONS

ONGLYZA is contraindicated in patients with a history of a serious hypersensitivity reaction to ONGLYZA, such as anaphylaxis, angioedema, or exfoliative skin conditions, or to any of the ingredients of this product. [See *Warnings and Precautions (5.4)* and *Adverse Reactions (6.2)*.]

5 WARNINGS AND PRECAUTIONS

5.1 Pancreatitis

There have been postmarketing reports of acute pancreatitis in patients taking ONGLYZA. In a cardiovascular outcomes trial enrolling participants with established atherosclerotic cardiovascular disease (ASCVD) or multiple risk factors for ASCVD (SAVOR trial), cases of definite acute pancreatitis were confirmed in 17 of 8240 (0.2%) patients receiving ONGLYZA compared to 9 of 8173 (0.1%) receiving placebo. Preexisting risk factors for pancreatitis were identified in 88% (15/17) of those patients receiving ONGLYZA and in 100% (9/9) of those patients receiving placebo.

After initiation of ONGLYZA, observe patients for signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue ONGLYZA and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using ONGLYZA.

5.2 Heart Failure

In a cardiovascular outcomes trial enrolling participants with established ASCVD or multiple risk factors for ASCVD (SAVOR trial), more patients randomized to ONGLYZA (289/8280, 3.5%) were hospitalized for heart failure compared to patients randomized to placebo (228/8212, 2.8%). In a time-to-first-event analysis the risk of hospitalization for heart failure was higher in the ONGLYZA group (estimated Hazard Ratio: 1.27; 95% CI: 1.07, 1.51). Subjects with a prior history of heart failure and subjects with renal impairment had a higher risk for hospitalization for heart failure, irrespective of treatment assignment.

Consider the risks and benefits of ONGLYZA prior to initiating treatment in patients at a higher risk for heart failure. Observe patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of ONGLYZA.

5.3 Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin

When ONGLYZA was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of confirmed hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. [See *Adverse Reactions (6.1)*.] Therefore, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia when used in combination with ONGLYZA. [See *Dosage and Administration (2.4)*.]

5.4 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with ONGLYZA. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with ONGLYZA, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue ONGLYZA, assess for other potential causes for the event, and institute alternative treatment for diabetes. [See *Adverse Reactions (6.2)*.]

Use caution in a patient with a history of angioedema to another dipeptidyl peptidase-4 (DPP4) inhibitor because it is unknown whether such patients will be predisposed to angioedema with ONGLYZA.

5.5 Severe and Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP4 inhibitor. Consider DPP4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

5.6 Bullous Pemphigoid

Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving ONGLYZA. If bullous pemphigoid is suspected, ONGLYZA should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

5.7 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Pancreatitis [see *Warnings and Precautions (5.1)*]
- Heart Failure [see *Warnings and Precautions (5.2)*]
- Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin [see *Warnings and Precautions (5.3)*]
- Hypersensitivity Reactions [see *Warnings and Precautions (5.4)*]
- Severe and disabling arthralgia [see *Warnings and Precautions (5.5)*]
- Bullous pemphigoid [see *Warnings and Precautions (5.6)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Efficacy Trials

The data in Table 1 are derived from a pool of 5 placebo-controlled clinical trials [*see Clinical Studies (14)*]. These data shown in the table reflect exposure of 882 patients to ONGLYZA and a mean duration of exposure to ONGLYZA of 21 weeks. The mean age of these patients was 55 years, 1.4 % were 75 years or older and 48.4% were male. The population was 67.5% White, 4.6% Black or African American, 17.4% Asian, Other 10.5% and 9.8% were of Hispanic or Latino ethnicity. At baseline the population had diabetes for an average of 5.2 years and a mean HbA1c of 8.2%. Baseline estimated renal function was normal or mildly impaired (eGFR≥60mL/min/1.73m^2) in 91% of these patients.

Table 1 shows common adverse reactions, excluding hypoglycemia, associated with the use of ONGLYZA. These adverse reactions occurred more commonly on ONGLYZA than on placebo and occurred in at least 5% of patients treated with ONGLYZA.

Table 1: Adverse Reactions in Placebo-Controlled Trials* Reported in ≥5% of Patients Treated with ONGLYZA 5 mg and More Commonly than in Patients Treated with Placebo

	% of Patients	
	ONGLYZA 5 mg N=882	**Placebo N=799**
Upper respiratory tract infection	7.7	7.6
Urinary tract infection	6.8	6.1
Headache	6.5	5.9

* The 5 placebo-controlled trials include two monotherapy trials and one add-on combination therapy trial with each of the following: metformin, thiazolidinedione, or glyburide. Table shows 24-week data regardless of glycemic rescue.

In patients treated with ONGLYZA 2.5 mg, headache (6.5%) was the only adverse reaction reported at a rate ≥5% and more commonly than in patients treated with placebo.

In this pooled analysis, adverse reactions that were reported in ≥2% of patients treated with ONGLYZA 2.5 mg or ONGLYZA 5 mg and ≥1% more frequently compared to placebo included: sinusitis (2.9% and 2.6% versus 1.6%, respectively), abdominal pain (2.4% and 1.7% versus 0.5%), gastroenteritis (1.9% and 2.3% versus 0.9%), and vomiting (2.2% and 2.3% versus 1.3%).

In the add-on to TZD trial, the incidence of peripheral edema was higher for ONGLYZA 5 mg versus placebo (8.1% and 4.3%, respectively). The incidence of peripheral edema for ONGLYZA 2.5 mg was 3.1%. None of the reported adverse reactions of peripheral edema resulted in study drug discontinuation. Rates of peripheral edema for ONGLYZA 2.5 mg and ONGLYZA 5 mg versus placebo were 3.6% and 2% versus 3% given as monotherapy, 2.1% and 2.1% versus 2.2% given as add-on therapy to metformin, and 2.4% and 1.2% versus 2.2% given as add-on therapy to glyburide.

The incidence rate of fractures was 1.0 and 0.6 per 100 patient-years, respectively, for ONGLYZA (pooled analysis of 2.5 mg, 5 mg, and 10 mg) and placebo. The 10mg dosage is not an approved dosage. The incidence rate of fracture events in patients who received ONGLYZA did not increase over time. Causality has not been established and nonclinical studies have not demonstrated adverse effects of ONGLYZA on bone.

An event of thrombocytopenia, consistent with a diagnosis of idiopathic thrombocytopenic purpura, was observed in the clinical program. The relationship of this event to ONGLYZA is not known.

Discontinuation of therapy due to adverse reactions occurred in 2.2%, 3.3%, and 1.8% of subjects receiving ONGLYZA 2.5 mg, ONGLYZA 5 mg, and placebo, respectively. The most common adverse reactions (reported in at least 2 subjects treated with ONGLYZA 2.5 mg or at least 2 subjects treated with ONGLYZA 5 mg) associated with premature discontinuation of therapy included lymphopenia (0.1% and 0.5% versus 0%, respectively), rash (0.2% and 0.3% versus 0.3%), blood creatinine increased (0.3% and 0% versus 0%), and blood creatine phosphokinase increased (0.1% and 0.2% versus 0%).

Adverse Reactions with Concomitant Use with Insulin

In the add-on to insulin trial [see *Clinical Studies (14.1)*], the incidence of adverse events, including serious adverse events and discontinuations due to adverse events, was similar between ONGLYZA and placebo, except for confirmed hypoglycemia [see *Adverse Reactions (6.1)*).

Adverse Reactions with Concomitant Use with Metformin in Treatment-Naive Patients with Type 2 Diabetes

Table 2 shows the adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients participating in an additional 24-week, active-controlled trial of coadministered ONGLYZA and metformin in treatment-naive patients.

Table 2: Initial Therapy with Combination of ONGLYZA and Metformin in Treatment-Naive Patients: Adverse Reactions Reported in ≥5% of Patients Treated with Combination Therapy of ONGLYZA 5 mg Plus Metformin (and More Commonly than in Patients Treated with Metformin Alone)

	Number (%) of Patients	
	ONGLYZA 5 mg + Metformin* N=320	**Metformin* N=328**
Headache	24 (7.5)	17 (5.2)
Nasopharyngitis	22 (6.9)	13 (4.0)

* Metformin was initiated at a starting dose of 500 mg daily and titrated up to a maximum of 2000 mg daily.

Hypoglycemia

Adverse reactions of hypoglycemia were based on all reports of hypoglycemia. A concurrent glucose measurement was not required or was normal in some patients. Therefore, it is not possible to conclusively determine that all these reports reflect true hypoglycemia.

In the add-on to glyburide study, the overall incidence of reported hypoglycemia was higher for ONGLYZA 2.5 mg and ONGLYZA 5 mg (13.3% and 14.6%) versus placebo (10.1%). The incidence of confirmed hypoglycemia in this study, defined as symptoms of hypoglycemia accompanied by a fingerstick glucose value of ≤50 mg/dL, was 2.4% and 0.8% for ONGLYZA 2.5 mg and ONGLYZA 5 mg and 0.7% for placebo [see *Warnings and Precautions (5.3)*]. The incidence of reported hypoglycemia for ONGLYZA 2.5 mg and ONGLYZA 5 mg versus placebo given as monotherapy was 4.0% and 5.6% versus 4.1%, respectively, 7.8% and 5.8% versus 5% given as add-on therapy to metformin, and 4.1% and 2.7% versus 3.8% given as add-on therapy to TZD. The incidence of reported hypoglycemia was 3.4% in treatment-naive patients given ONGLYZA 5 mg plus metformin and 4.0% in patients given metformin alone.

In the active-controlled trial comparing add-on therapy with ONGLYZA 5 mg to glipizide in patients inadequately controlled on metformin alone, the incidence of reported hypoglycemia was 3% (19 events in 13 patients) with ONGLYZA 5 mg versus 36.3% (750 events in 156 patients) with glipizide. Confirmed symptomatic hypoglycemia (accompanying fingerstick blood glucose ≤50 mg/dL) was reported in none of the ONGLYZA-treated patients and in 35 glipizide-treated patients (8.1%) ($p<0.0001$).

In the add-on to insulin trial, the overall incidence of reported hypoglycemia was 18.4% for ONGLYZA 5 mg and 19.9% for placebo. However, the incidence of confirmed symptomatic hypoglycemia (accompanying fingerstick blood glucose ≤50 mg/dL) was higher with ONGLYZA 5 mg (5.3%) versus placebo (3.3%).

In the add-on to metformin plus sulfonylurea trial, the overall incidence of reported hypoglycemia was 10.1% for ONGLYZA 5mg and 6.3% for placebo. Confirmed hypoglycemia was reported in 1.6% of the ONGLYZA-treated patients and in none of the placebo-treated patients [see *Warnings and Precautions (5.3)*].

Hypersensitivity Reactions

Hypersensitivity-related events, such as urticaria and facial edema in the 5-study pooled analysis up to Week 24 were reported in 1.5%, 1.5%, and 0.4% of patients who received ONGLYZA 2.5 mg, ONGLYZA 5 mg, and placebo, respectively. None of these events in patients who received ONGLYZA required hospitalization or were reported as life-threatening by the investigators. One ONGLYZA-treated patient in this pooled analysis discontinued due to generalized urticaria and facial edema.

Renal Impairment

In the SAVOR trial, adverse reactions related to renal impairment, including laboratory changes (i.e., doubling of serum creatinine compared with baseline and serum creatinine >6 mg/dL), were reported in 5.8% (483/8280) of ONGLYZA-treated subjects and 5.1% (422/8212) of placebo-treated subjects. The most frequently reported adverse reactions included renal impairment (2.1% vs. 1.9%), acute renal failure (1.4% vs. 1.2%), and renal failure (0.8% vs. 0.9%), in the ONGLYZA versus placebo groups, respectively. From baseline to the end of treatment, there was a mean decrease in eGFR of 2.5 mL/min/1.73m2 for ONGLYZA-treated patients and a mean decrease of 2.4 mL/min/1.73m2 for placebo-treated patients. More subjects randomized to ONGLYZA (421/5227, 8.1%) compared to subjects randomized to placebo (344/5073, 6.8%) had downward shifts in eGFR from >50 mL/min (i.e., normal or mild renal impairment) to ≤50 mL/min (i.e., moderate or severe renal impairment). The proportions of subjects with renal adverse reactions increased with worsening baseline renal function and increased age, regardless of treatment assignment.

Infections

In the unblinded, controlled, clinical trial database for ONGLYZA to date, there have been 6 (0.12%) reports of tuberculosis among the 4959 ONGLYZA-treated patients (1.1 per 1000 patient-years) compared to no reports of tuberculosis among the 2868 comparator-treated patients. Two of these six cases were confirmed with laboratory testing. The remaining cases had limited information or had presumptive diagnoses of tuberculosis. None of the six cases occurred in the United States or in Western Europe. One case occurred in Canada in a patient originally from Indonesia who had recently visited Indonesia. The duration of treatment with ONGLYZA until report of tuberculosis ranged from 144 to 929 days. Post-treatment lymphocyte counts were consistently within the reference range for four cases. One patient had lymphopenia prior to initiation of ONGLYZA that remained stable throughout ONGLYZA treatment. The final patient had an isolated lymphocyte count below normal approximately four months prior to the report of tuberculosis. There have been no spontaneous reports of tuberculosis associated with ONGLYZA use. Causality has not been estimated and there are too few cases to date to determine whether tuberculosis is related to ONGLYZA use.

There has been one case of a potential opportunistic infection in the unblinded, controlled clinical trial database to date in a ONGLYZA-treated patient who developed suspected foodborne fatal salmonella sepsis after approximately 600 days of ONGLYZA therapy. There have been no spontaneous reports of opportunistic infections associated with ONGLYZA use.

Vital Signs

No clinically meaningful changes in vital signs have been observed in patients treated with ONGLYZA.

Laboratory Tests

Absolute Lymphocyte Counts

There was a dose-related mean decrease in absolute lymphocyte count observed with ONGLYZA. From a baseline mean absolute lymphocyte count of approximately 2200 cells/microL, mean decreases of approximately 100 and 120 cells/microL with ONGLYZA 5 mg and 10 mg, respectively, relative to placebo were observed at 24 weeks in a pooled analysis of five placebo-controlled clinical studies. Similar effects were observed when ONGLYZA 5 mg was given in initial combination with metformin compared to metformin alone. There was no difference observed for ONGLYZA 2.5 mg relative to placebo. The proportion of patients who were reported to have a lymphocyte count ≤750 cells/microL was 0.5%, 1.5%, 1.4%, and 0.4% in the ONGLYZA 2.5 mg, 5 mg, 10 mg, and placebo groups, respectively. In most patients, recurrence was not observed with repeated exposure to ONGLYZA although some patients had recurrent decreases upon rechallenge that led to discontinuation of ONGLYZA. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions. The 10mg dosage is not an approved dosage.

In the SAVOR trial mean decreases of approximately 84 cells/microL with ONGLYZA relative to placebo was observed. The proportion of patients who experienced a decrease in lymphocyte counts to a count of ≤750 cells/microL was 1.6% (136/8280) and 1.0% (78/8212) on ONGLYZA and placebo respectively.

The clinical significance of this decrease in lymphocyte count relative to placebo is not known. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured. The effect of ONGLYZA on lymphocyte counts in patients with lymphocyte abnormalities (e.g., human immunodeficiency virus) is unknown.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during post-approval use of ONGLYZA. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions. [See *Contraindications (4)* and *Warnings and Precautions (5.4)*.]
- Pancreatitis. [See *Warnings and Precautions (5.1*).]
- Severe and disabling arthralgia [*see Warnings and Precautions (5.5)*].
- Bullous pemphigoid [see *Warnings and Precautions (5.6)*]

7 DRUG INTERACTIONS

7.1 Strong Inhibitors of CYP3A4/5 Enzymes

Ketoconazole significantly increased saxagliptin exposure. Similar significant increases in plasma concentrations of saxagliptin are anticipated with other strong CYP3A4/5 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin). The dose of ONGLYZA should be limited to 2.5 mg when coadministered with a strong CYP3A4/5 inhibitor. [See *Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)*.]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited data with ONGLYZA in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriages. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [see *Clinical Considerations*].

No adverse developmental effects independent of maternal toxicity were observed when saxagliptin was administered to pregnant rats and rabbits during the period of organogenesis and in pregnant and lactating rats during the pre- and postnatal period [see *Data*].

The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes with an HbA1c greater than 7 and has been reported to be as high as 20 to 25% in women with an HbA1c greater than 10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, still birth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

In embryo-fetal development studies, saxagliptin was administered to pregnant rats and rabbits during the period of organogenesis, corresponding to the first trimester of human pregnancy. No adverse developmental effects were observed in either species at exposures 1503- and 152-times the 5 mg clinical dose in rats and rabbits, respectively, based on AUC. Saxagliptin crosses the placenta into the fetus following dosing in pregnant rats.

In a prenatal and postnatal development study, no adverse developmental effects were observed in maternal rats administered saxagliptin from gestation day 6 through lactation day 21 at exposures up to 470-times the 5 mg clinical dose, based on AUC.

8.2 Lactation

Risk Summary

There is no information regarding the presence of ONGLYZA in human milk, the effects on the breastfed infant, or the effects on milk production.

Saxagliptin is present in the milk of lactating rats [see *Data*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ONGLYZA and any potential adverse effects on the breastfed infant from ONGLYZA or from the underlying maternal condition.

Data

Saxagliptin is secreted in the milk of lactating rats at approximately a 1:1 ratio with plasma drug concentrations.

8.4 Pediatric Use

Safety and effectiveness of ONGLYZA in pediatric patients under 18 years of age have not been established. Additionally, studies characterizing the pharmacokinetics of ONGLYZA in pediatric patients have not been performed.

8.5 Geriatric Use

In the seven, double-blind, controlled clinical safety and efficacy trials of ONGLYZA, a total of 4751 (42.0%) of the 11301 patients randomized to ONGLYZA were 65 years and over, and 1210 (10.7%) were 75 years and over. No overall differences in safety or effectiveness were observed between subjects ≥65 years old and younger subjects. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Saxagliptin and its active metabolite are eliminated in part by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly based on renal function. [See *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3).*]

8.6 Renal Impairment

In a 12-week randomized placebo-controlled trial, ONGLYZA 2.5 mg was administered to 85 subjects with moderate (n=48) or severe (n=18) renal impairment or end-stage renal disease (ESRD) (n=19) [*see Clinical Studies (14)*]. The incidence of adverse events, including serious adverse events and discontinuations due to adverse events, was similar between ONGLYZA and placebo. The overall incidence of reported hypoglycemia was 20% among subjects treated with ONGLYZA 2.5 mg and 22% among subjects treated with placebo. Four ONGLYZA-treated subjects (4.7%) and three placebo-treated subjects (3.5%) reported at least one episode of confirmed symptomatic hypoglycemia (accompanying fingerstick glucose ≤50 mg/dL).

10 OVERDOSAGE

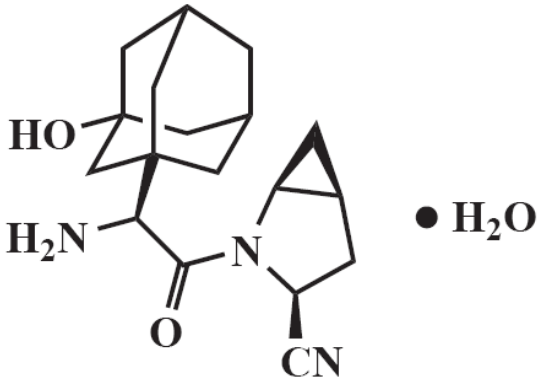
In a controlled clinical trial, once-daily, orally-administered ONGLYZA in healthy subjects at doses up to 400 mg daily for 2 weeks (80 times the MRHD) had no dose-related clinical adverse reactions and no clinically meaningful effect on QTc interval or heart rate.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its active metabolite are removed by hemodialysis (23% of dose over 4 hours).

11 DESCRIPTION

Saxagliptin is an orally-active inhibitor of the DPP4 enzyme.

Saxagliptin monohydrate is described chemically as (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate or (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrate. The empirical formula is $C_{18}H_{25}N_3O_2 \bullet H_2O$ and the molecular weight is 333.43. The structural formula is:



Saxagliptin monohydrate is a white to light yellow or light brown, non-hygroscopic, crystalline powder. It is sparingly soluble in water at 24°C ± 3°C, slightly soluble in ethyl acetate, and soluble in methanol, ethanol, isopropyl alcohol, acetonitrile, acetone, and polyethylene glycol 400 (PEG 400).

Each film-coated tablet of ONGLYZA for oral use contains either 2.79 mg saxagliptin hydrochloride (anhydrous) equivalent to 2.5 mg saxagliptin or 5.58 mg saxagliptin hydrochloride (anhydrous) equivalent to 5 mg saxagliptin and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and iron oxides.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Increased concentrations of the incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released into the bloodstream from the small intestine in response to meals. These hormones cause insulin release from the pancreatic beta cells in a glucose-dependent

manner but are inactivated by the DPP4 enzyme within minutes. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, reducing hepatic glucose production. In patients with type 2 diabetes, concentrations of GLP-1 are reduced but the insulin response to GLP-1 is preserved. Saxagliptin is a competitive DPP4 inhibitor that slows the inactivation of the incretin hormones, thereby increasing their bloodstream concentrations and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with type 2 diabetes mellitus.

12.2 Pharmacodynamics

In patients with type 2 diabetes mellitus, administration of ONGLYZA inhibits DPP4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased glucose-dependent insulin secretion from pancreatic beta cells. The rise in insulin and decrease in glucagon were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

Cardiac Electrophysiology

In a randomized, double-blind, placebo-controlled, 4-way crossover, active comparator study using moxifloxacin in 40 healthy subjects, ONGLYZA was not associated with clinically meaningful prolongation of the QTc interval or heart rate at daily doses up to 40 mg (8 times the MRHD).

12.3 Pharmacokinetics

The pharmacokinetics of saxagliptin and its active metabolite, 5-hydroxy saxagliptin were similar in healthy subjects and in patients with type 2 diabetes mellitus. The C_{max} and AUC values of saxagliptin and its active metabolite increased proportionally in the 2.5 to 400 mg dose range. Following a 5 mg single oral dose of saxagliptin to healthy subjects, the mean plasma AUC values for saxagliptin and its active metabolite were 78 ng•h/mL and 214 ng•h/mL, respectively. The corresponding plasma C_{max} values were 24 ng/mL and 47 ng/mL, respectively. The average variability (%CV) for AUC and C_{max} for both saxagliptin and its active metabolite was less than 25%.

No appreciable accumulation of either saxagliptin or its active metabolite was observed with repeated once-daily dosing at any dose level. No dose- and time-dependence were observed in the clearance of saxagliptin and its active metabolite over 14 days of once-daily dosing with saxagliptin at doses ranging from 2.5 to 400 mg.

Absorption

The median time to maximum concentration (T_{max}) following the 5 mg once daily dose was 2 hours for saxagliptin and 4 hours for its active metabolite. Administration with a high-fat meal resulted in an increase in T_{max} of saxagliptin by approximately 20 minutes as compared to fasted conditions. There was a 27% increase in the AUC of saxagliptin when given with a meal as compared to fasted conditions. ONGLYZA may be administered with or without food.

Distribution

The *in vitro* protein binding of saxagliptin and its active metabolite in human serum is negligible. Therefore, changes in blood protein levels in various disease states (e.g., renal or hepatic impairment) are not expected to alter the disposition of saxagliptin.

Metabolism

The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). The major metabolite of saxagliptin is also a DPP4 inhibitor, which is one-half as potent as saxagliptin. Therefore, strong CYP3A4/5 inhibitors and inducers will alter the pharmacokinetics of saxagliptin and its active metabolite. [See *Drug Interactions (7.1)*.]

Excretion

Saxagliptin is eliminated by both renal and hepatic pathways. Following a single 50 mg dose of ^{14}C-saxagliptin, 24%, 36%, and 75% of the dose was excreted in the urine as saxagliptin, its active metabolite, and total radioactivity, respectively. The average renal clearance of saxagliptin (~230 mL/min) was greater than the average estimated glomerular filtration rate (~120 mL/min), suggesting some active renal excretion. A total of 22% of the administered radioactivity was recovered in feces representing the fraction of the saxagliptin dose excreted in bile and/or unabsorbed drug from the gastrointestinal tract. Following a single oral dose of ONGLYZA 5 mg to healthy subjects, the mean plasma terminal half-life ($t_{1/2}$) for saxagliptin and its active metabolite was 2.5 and 3.1 hours, respectively.

Specific Populations

Renal Impairment

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of saxagliptin (10 mg dose) in subjects with varying degrees of chronic renal impairment compared to subjects with normal renal function. The 10mg dosage is not an approved dosage. The degree of renal impairment did not affect C_{max} of saxagliptin or its metabolite. In subjects with moderate renal impairment with (eGFR 30 to less than 45 mL/min/1.73m^2), severe renal impairment (eGFR 15 to less than 30 mL/min/1.73m^2) and ESRD patient on hemodialysis, the AUC values of saxagliptin or its metabolite were >2 fold higher than AUC values in subjects with normal renal function.

Hepatic Impairment

In subjects with hepatic impairment (Child-Pugh classes A, B, and C), mean C_{max} and AUC of saxagliptin were up to 8% and 77% higher, respectively, compared to healthy matched controls following administration of a single 10 mg dose of saxagliptin. The 10mg dosage is not an approved dosage. The corresponding C_{max} and AUC of the active metabolite were up to 59% and 33% lower, respectively, compared to healthy matched controls. These differences are not considered to be clinically meaningful.

Body Mass Index

No dosage adjustment is recommended based on body mass index (BMI) which was not identified as a significant covariate on the apparent clearance of saxagliptin or its active metabolite in the population pharmacokinetic analysis.

Gender

No dosage adjustment is recommended based on gender. There were no differences observed in saxagliptin pharmacokinetics between males and females. Compared to males, females had approximately 25% higher exposure values for the active metabolite than males, but this difference is unlikely to be of clinical relevance. Gender was not identified as a significant covariate on the apparent clearance of saxagliptin and its active metabolite in the population pharmacokinetic analysis.

Geriatric

No dosage adjustment is recommended based on age alone. Elderly subjects (65-80 years) had 23% and 59% higher geometric mean C_{max} and geometric mean AUC values, respectively, for saxagliptin than young subjects (18-40 years). Differences in active metabolite pharmacokinetics between elderly and young subjects generally reflected the differences observed in saxagliptin pharmacokinetics. The difference between the pharmacokinetics of saxagliptin and the active metabolite in young and elderly subjects is likely due to multiple factors including declining renal function and metabolic capacity with increasing age. Age was not identified as a significant covariate on the apparent clearance of saxagliptin and its active metabolite in the population pharmacokinetic analysis.

Race and Ethnicity

No dosage adjustment is recommended based on race. The population pharmacokinetic analysis compared the pharmacokinetics of saxagliptin and its active metabolite in 309 Caucasian subjects with 105 non-Caucasian subjects (consisting of six racial groups). No significant difference in the pharmacokinetics of saxagliptin and its active metabolite were detected between these two populations.

Drug-Drug Interaction Studies

In Vitro Assessment of Drug Interactions

The metabolism of saxagliptin is primarily mediated by CYP3A4/5.

In *in vitro* studies, saxagliptin and its active metabolite did not inhibit CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4, or induce CYP1A2, 2B6, 2C9, or 3A4. Therefore, saxagliptin is not expected to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes. Saxagliptin is a P-glycoprotein (P-gp) substrate but is not a significant inhibitor or inducer of P-gp.

In Vivo Assessment of Drug Interactions

Table 3: Effect of Coadministered Drugs on Systemic Exposures of Saxagliptin and its Active Metabolite, 5-hydroxy Saxagliptin

Coadministered Drug	Dosage of Coadministered Drug*	Dosage of Saxagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00		
				AUC†	C_{max}
No dosing adjustments required for the following:					
Metformin	1000 mg	100 mg	saxagliptin 5-hydroxy saxagliptin	0.98 0.99	0.79 0.88
Glyburide	5 mg	10 mg	saxagliptin 5-hydroxy saxagliptin	0.98 ND	1.08 ND
Dapagliflozin	10 mg single dose	5 mg single dose	saxagliptin 5-hydroxy saxagliptin	↓1% ↑9%	↓7% ↑6%
Pioglitazone‡	45 mg QD for 10 days	10 mg QD for 5 days	saxagliptin 5-hydroxy saxagliptin	1.11 ND	1.11 ND
Digoxin	0.25 mg q6h first day followed by q12h second day followed by QD for 5 days	10 mg QD for 7 days	saxagliptin 5-hydroxy saxagliptin	1.05 1.06	0.99 1.02
Simvastatin	40 mg QD for 8 days	10 mg QD for 4 days	saxagliptin 5-hydroxy saxagliptin	1.12 1.02	1.21 1.08
Diltiazem	360 mg LA QD for 9 days	10 mg	saxagliptin 5-hydroxy saxagliptin	2.09 0.66	1.63 0.57
Rifampin§	600 mg QD for 6 days	5 mg	saxagliptin 5-hydroxy saxagliptin	0.24 1.03	0.47 1.39
Omeprazole	40 mg QD for 5 days	10 mg	saxagliptin 5-hydroxy saxagliptin	1.13 ND	0.98 ND
Aluminum hydroxide + magnesium hydroxide + simethicone	aluminum hydroxide: 2400 mg magnesium hydroxide: 2400 mg simethicone: 240 mg	10 mg	saxagliptin 5-hydroxy saxagliptin	0.97 ND	0.74 ND
Famotidine	40 mg	10 mg	saxagliptin 5-hydroxy saxagliptin	1.03 ND	1.14 ND
Limit ONGLYZA dose to 2.5 mg once daily when coadministered with strong CYP3A4/5 inhibitors *[see Drug Interactions (7.1) and Dosage and Administration (2.3)]*:					
Ketoconazole	200 mg BID for 9 days	100 mg	saxagliptin 5-hydroxy saxagliptin	2.45 0.12	1.62 0.05
Ketoconazole	200 mg BID for 7 days	20 mg	saxagliptin 5-hydroxy saxagliptin	3.67 ND	2.44 ND

* Single dose unless otherwise noted. The 10 mg saxagliptin dose is not an approved dosage.

† AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses

‡ Results exclude one subject

§ The plasma dipeptidyl peptidase-4 (DPP4) activity inhibition over a 24-hour dose interval was not affected by rifampin

ND=not determined; QD=once daily; q6h=every 6 hours; q12h=every 12 hours; BID=twice daily; LA=long acting

Table 4: Effect of Saxagliptin on Systemic Exposures of Coadministered Drugs

Coadministered Drug	Dosage of Coadministered Drug*	Dosage of Saxagliptin*	Geometric Mean Ratio (ratio with/without saxagliptin) No Effect = 1.00		
				AUC†	C_{max}
No dosing adjustments required for the following:					
Metformin	1000 mg	100 mg	metformin	1.20	1.09
Glyburide	5 mg	10 mg	glyburide	1.06	1.16
Pioglitazone‡	45 mg QD for 10 days	10 mg QD for 5 days	pioglitazone hydroxy-pioglitazone	1.08 ND	1.14 ND
Digoxin	0.25 mg q6h first day followed by q12h second day followed by QD for 5 days	10 mg QD for 7 days	digoxin	1.06	1.09
Simvastatin	40 mg QD for 8 days	10 mg QD for 4 days	simvastatin simvastatin acid	1.04 1.16	0.88 1.00
Diltiazem	360 mg LA QD for 9 days	10 mg	diltiazem	1.10	1.16
Ketoconazole	200 mg BID for 9 days	100 mg	ketoconazole	0.87	0.84
Ethinyl estradiol and Norgestimate	ethinyl estradiol 0.035 mg and norgestimate 0.250 mg for 21 days	5 mg QD for 21 days	ethinyl estradiol norelgestromin norgestrel	1.07 1.10 1.13	0.98 1.09 1.17

* Single dose unless otherwise noted. The 10 mg and 100 mg saxagliptin doses are not approved dosages.

† AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses

‡ Results include all subjects

ND=not determined; QD=once daily; q6h=every 6 hours; q12h=every 12 hours; BID=twice daily; LA=long acting

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity was evaluated in 2-year studies conducted in CD-1 mice and Sprague-Dawley rats. Saxagliptin did not increase the incidence of tumors in mice dosed orally at 50, 250, and 600 mg/kg up to 870-times (males) and 1165-times (females) the 5 mg/day clinical dose, based on AUC. Saxagliptin did not increase the incidence of tumors in rats dosed orally at 25, 75, 150, and 300 mg/kg up to 355-times (males) and 2217-times (females) the 5 mg/day clinical dose, based on AUC.

Mutagenesis

Saxagliptin was not mutagenic or clastogenic in a battery of genotoxicity tests (Ames bacterial mutagenesis, human and rat lymphocyte cytogenetics, rat bone marrow micronucleus and DNA repair assays). The active metabolite of saxagliptin was not mutagenic in an Ames bacterial assay.

Impairment of Fertility

Saxagliptin administered to rats had no effect on fertility or the ability to maintain a litter at exposures up to 603-times and 776-times the 5mg clinical dose in males and females, based on AUC.

13.2 Animal Toxicology and/or Pharmacology

Saxagliptin produced adverse skin changes in the extremities of cynomolgus monkeys (scabs and/or ulceration of tail, digits, scrotum, and/or nose). Skin lesions were reversible within exposure approximately 20-times the 5 mg clinical dose, but in some cases were irreversible and necrotizing at higher exposures. Adverse skin changes were not observed at exposures similar to (1 to 3 times) the 5 mg clinical dose. Clinical correlates to skin lesions in monkeys have not been observed in human clinical trials of saxagliptin.

14 CLINICAL STUDIES

14.1 Glycemic Efficacy Trials

ONGLYZA has been studied as monotherapy and in combination with metformin, glyburide, and thiazolidinedione (pioglitazone and rosiglitazone) therapy.

A total of 4148 patients with type 2 diabetes mellitus were randomized in six, double-blind, controlled clinical trials conducted to evaluate the safety and glycemic efficacy of ONGLYZA. A total of 3021 patients in these trials were treated with ONGLYZA. In these trials, the mean age was 54 years, and 71% of patients were Caucasian, 16% were Asian, 4% were black, and 9% were of other racial groups. An additional 423 patients, including 315 who received ONGLYZA, participated in a placebo-controlled, dose-ranging study of 6 to 12 weeks in duration.

In these six, double-blind trials, ONGLYZA was evaluated at doses of 2.5 mg and 5 mg once daily. Three of these trials also evaluated an ONGLYZA dose of 10 mg daily. The 10 mg daily dose of ONGLYZA did not provide greater efficacy than the 5 mg daily dose. The 10mg dosage is not an approved dosage. Treatment with ONGLYZA 5 mg and 2.5 mg doses produced clinically relevant and statistically significant improvements in A1C, fasting plasma glucose (FPG), and 2-hour postprandial glucose (PPG) following a standard oral glucose tolerance test (OGTT), compared to control. Reductions in A1C were seen across subgroups including gender, age, race, and baseline BMI.

ONGLYZA was not associated with significant changes from baseline in body weight or fasting serum lipids compared to placebo.

ONGLYZA has also been evaluated in five additional trials in patients with type 2 diabetes: an active-controlled trial comparing add-on therapy with ONGLYZA to glipizide in 858 patients inadequately controlled on metformin alone, a trial comparing ONGLYZA to placebo in 455 patients inadequately controlled on insulin alone or on insulin in combination with metformin, a trial comparing ONGLYZA to placebo in 257 patients inadequately controlled on metformin plus a sulfonylurea, a trial comparing ONGLYZA to placebo in 315 patients inadequately controlled on dapagliflozin and metformin, and a trial comparing ONGLYZA to placebo in 170 patients with type 2 diabetes and moderate or severe renal impairment or ESRD.

Monotherapy

A total of 766 patients with type 2 diabetes inadequately controlled on diet and exercise (A1C ≥7% to ≤10%) participated in two 24-week, double-blind, placebo-controlled trials evaluating the efficacy and safety of ONGLYZA monotherapy.

In the first trial, following a 2-week single-blind diet, exercise, and placebo lead-in period, 401 patients were randomized to 2.5 mg, 5 mg, or 10 mg of ONGLYZA or placebo. The 10mg dosage is not an approved dosage. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue therapy, added on to placebo or ONGLYZA. Efficacy was evaluated at the last measurement prior to rescue therapy for patients needing rescue. Dose titration of ONGLYZA was not permitted.

Treatment with ONGLYZA 2.5 mg and 5 mg daily provided significant improvements in A1C, FPG, and PPG compared to placebo (Table 4). The percentage of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 16% in the ONGLYZA 2.5 mg treatment group, 20% in the ONGLYZA 5 mg treatment group, and 26% in the placebo group.

Table 5: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA Monotherapy in Patients with Type 2 Diabetes*

Efficacy Parameter	**ONGLYZA 2.5 mg N=102**	**ONGLYZA 5 mg N=106**	**Placebo N=95**
Hemoglobin A1C (%)	**N=100**	**N=103**	**N=92**
Baseline (mean)	7.9	8.0	7.9
Change from baseline (adjusted mean†)	–0.4	–0.5	+0.2
Difference from placebo (adjusted mean†)	–0.6‡	–0.6‡	
95% Confidence Interval	(−0.9, −0.3)	(−0.9, −0.4)	
Percent of patients achieving A1C <7%	35% (35/100)	38%§ (39/103)	24% (22/92)
Fasting Plasma Glucose (mg/dL)	**N=101**	**N=105**	**N=92**
Baseline (mean)	178	171	172
Change from baseline (adjusted mean†)	−15	−9	+6
Difference from placebo (adjusted mean†)	−21§	−15§	
95% Confidence Interval	(−31, −10)	(−25, −4)	
2-hour Postprandial Glucose (mg/dL)	**N=78**	**N=84**	**N=71**
Baseline (mean)	279	278	283
Change from baseline (adjusted mean†)	−45	−43	−6
Difference from placebo (adjusted mean†)	−39¶	−37§	
95% Confidence Interval	(−61, −16)	(−59, −15)	

* Intent-to-treat population using last observation on study or last observation prior to metformin rescue therapy for patients needing rescue

† Least squares mean adjusted for baseline value

‡ p-value <0.0001 compared to placebo

§ p-value <0.05 compared to placebo

¶ Significance was not tested for the 2-hour PPG for the 2.5 mg dose of ONGLYZA

A second 24-week monotherapy trial was conducted to assess a range of dosing regimens for ONGLYZA. Treatment-naive patients with inadequately controlled diabetes (A1C ≥7% to ≤10%) underwent a 2-week, single-blind diet, exercise, and placebo lead-in period. A total of 365 patients were randomized to 2.5 mg every morning, 5 mg every morning, 2.5 mg with possible titration to 5 mg every morning, or 5 mg every evening of ONGLYZA, or placebo. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue therapy added on to placebo or ONGLYZA; the number of patients randomized per treatment group ranged from 71 to 74.

Treatment with either ONGLYZA 5 mg every morning or 5 mg every evening provided significant improvements in A1C versus placebo (mean placebo-corrected reductions of –0.4% and –0.3%, respectively). Treatment with ONGLYZA 2.5 mg every morning also provided significant improvement in A1C versus placebo (mean placebo-corrected reduction of –0.4%).

Combination Therapy

Add-On Combination Therapy with Metformin

A total of 743 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with metformin in patients with inadequate glycemic control (A1C ≥7% and ≤10%) on metformin alone. To qualify for enrollment, patients were required to be on a stable dose of metformin (1500-2550 mg daily) for at least 8 weeks.

Patients who met eligibility criteria were enrolled in a single-blind, 2-week, dietary and exercise placebo lead-in period during which patients received metformin at their pre-study dose, up to 2500 mg daily. Following the lead-in period, eligible patients were randomized to 2.5 mg, 5 mg, or 10 mg of ONGLYZA or placebo in addition to their current dose of open-label metformin. The 10 mg dosage is not an approved dosage. Patients who failed to meet specific glycemic goals during the study were treated with pioglitazone rescue therapy, added on to existing study medications. Dose titrations of ONGLYZA and metformin were not permitted.

ONGLYZA 2.5 mg and 5 mg add-on to metformin provided significant improvements in A1C, FPG, and PPG compared with placebo add-on to metformin (Table 5). Mean changes from baseline for A1C over time and at endpoint are shown in Figure 1. The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 15% in the ONGLYZA 2.5 mg add-on to metformin group, 13% in the ONGLYZA 5 mg add-on to metformin group, and 27% in the placebo add-on to metformin group.

Table 6: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA as Add-On Combination Therapy with Metformin*

Efficacy Parameter	ONGLYZA 2.5 mg + Metformin N=192	ONGLYZA 5 mg + Metformin N=191	Placebo + Metformin N=179
Hemoglobin A1C (%)	**N=186**	**N=186**	**N=175**
Baseline (mean)	8.1	8.1	8.1
Change from baseline (adjusted mean†)	−0.6	−0.7	+0.1
Difference from placebo (adjusted mean†)	−0.7‡	−0.8‡	
95% Confidence Interval	(−0.9, −0.5)	(−1.0, −0.6)	
Percent of patients achieving A1C <7%	37%§ (69/186)	44%§ (81/186)	17% (29/175)
Fasting Plasma Glucose (mg/dL)	**N=188**	**N=187**	**N=176**
Baseline (mean)	174	179	175
Change from baseline (adjusted mean†)	−14	−22	+1
Difference from placebo (adjusted mean†)	−16§	−23§	
95% Confidence Interval	(−23, −9)	(−30, −16)	
2-hour Postprandial Glucose (mg/dL)	**N=155**	**N=155**	**N=135**
Baseline (mean)	294	296	295
Change from baseline (adjusted mean†)	−62	−58	−18
Difference from placebo (adjusted mean†)	−44§	−40§	
95% Confidence Interval	(−60, −27)	(−56, −24)	

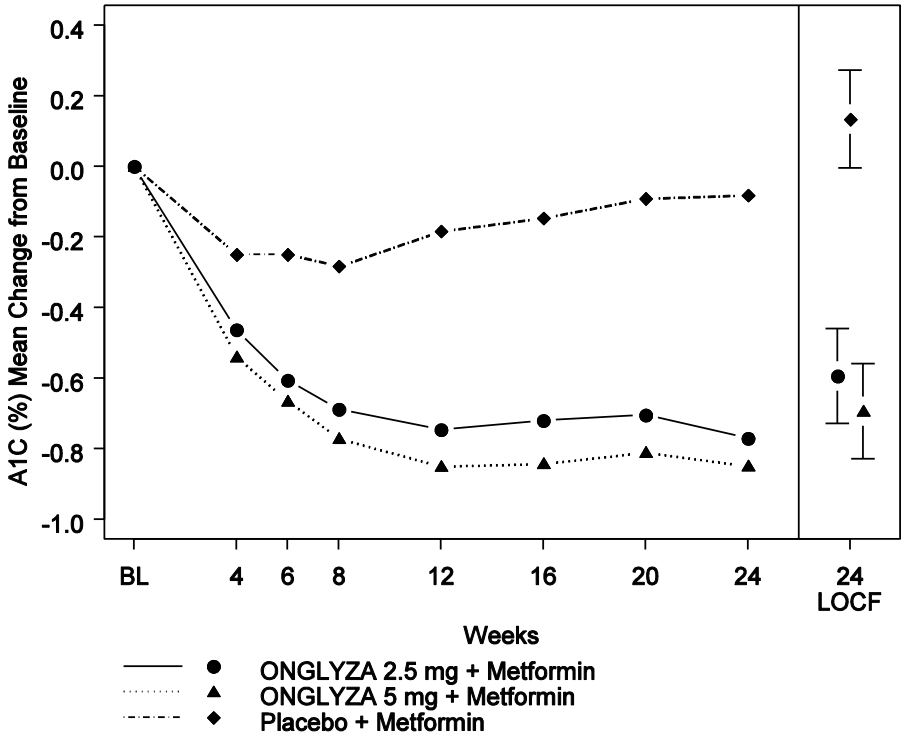
* Intent-to-treat population using last observation on study or last observation prior to pioglitazone rescue therapy for patients needing rescue

† Least squares mean adjusted for baseline value

‡ p-value <0.0001 compared to placebo + metformin

§ p-value <0.05 compared to placebo + metformin

Figure 1: Mean Change from Baseline in A1C in a Placebo-Controlled Trial of ONGLYZA as Add-On Combination Therapy with Metformin*



* Includes patients with a baseline and week 24 value.
Week 24 (LOCF) includes intent-to-treat population using last observation on study prior to pioglitazone rescue therapy for patients needing rescue. Mean change from baseline is adjusted for baseline value.

Add-On Combination Therapy with a Thiazolidinedione

A total of 565 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with a thiazolidinedione (TZD) in patients with inadequate glycemic control (A1C ≥7% to ≤10.5%) on TZD alone. To qualify for enrollment, patients were required to be on a stable dose of pioglitazone (30-45 mg once daily) or rosiglitazone (4 mg once daily or 8 mg either once daily or in two divided doses of 4 mg) for at least 12 weeks.

Patients who met eligibility criteria were enrolled in a single-blind, 2-week, dietary and exercise placebo lead-in period during which patients received TZD at their pre-study dose. Following the lead-in period, eligible patients were randomized to 2.5 mg or 5 mg of ONGLYZA or placebo in addition to their current dose of TZD. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue, added on to existing study medications. Dose titration of ONGLYZA or TZD was not permitted during the study. A change in TZD regimen from rosiglitazone to pioglitazone at specified, equivalent therapeutic doses was permitted at the investigator's discretion if believed to be medically appropriate.

ONGLYZA 2.5 mg and 5 mg add-on to TZD provided significant improvements in A1C, FPG, and PPG compared with placebo add-on to TZD (Table 6). The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 10% in the ONGLYZA

2.5 mg add-on to TZD group, 6% for the ONGLYZA 5 mg add-on to TZD group, and 10% in the placebo add-on to TZD group.

Table 7: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA as Add-On Combination Therapy with a Thiazolidinedione*

Efficacy Parameter	ONGLYZA 2.5 mg + TZD N=195	ONGLYZA 5 mg + TZD N=186	Placebo + TZD N=184
Hemoglobin A1C (%)	**N=192**	**N=183**	**N=180**
Baseline (mean)	8.3	8.4	8.2
Change from baseline (adjusted mean†)	−0.7	−0.9	−0.3
Difference from placebo (adjusted mean†)	−0.4§	−0.6‡	
95% Confidence Interval	(−0.6, −0.2)	(−0.8, −0.4)	
Percent of patients achieving A1C <7%	42%§ (81/192)	42%§ (77/184)	26% (46/180)
Fasting Plasma Glucose (mg/dL)	**N=193**	**N=185**	**N=181**
Baseline (mean)	163	160	162
Change from baseline (adjusted mean†)	−14	−17	−3
Difference from placebo (adjusted mean†)	−12§	−15§	
95% Confidence Interval	(−20, −3)	(−23, −6)	
2-hour Postprandial Glucose (mg/dL)	**N=156**	**N=134**	**N=127**
Baseline (mean)	296	303	291
Change from baseline (adjusted mean†)	−55	−65	−15
Difference from placebo (adjusted mean†)	−40§	−50§	
95% Confidence Interval	(−56, −24)	(−66, −34)	

* Intent-to-treat population using last observation on study or last observation prior to metformin rescue therapy for patients needing rescue

† Least squares mean adjusted for baseline value

‡ p-value <0.0001 compared to placebo + TZD

§ p-value <0.05 compared to placebo + TZD

Add-On Combination Therapy with Glyburide

A total of 768 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with a sulfonylurea (SU) in patients with inadequate glycemic control at enrollment (A1C ≥7.5% to ≤10%) on a submaximal dose of SU alone. To qualify for enrollment, patients were required to be on a submaximal dose of SU for 2 months or greater. In this study, ONGLYZA in combination with a fixed, intermediate dose of SU was compared to titration to a higher dose of SU.

Patients who met eligibility criteria were enrolled in a single-blind, 4-week, dietary and exercise lead-in period, and placed on glyburide 7.5 mg once daily. Following the lead-in period, eligible patients with A1C ≥7% to ≤10% were randomized to either 2.5 mg or 5 mg of ONGLYZA add-on to 7.5 mg glyburide or to placebo plus a 10 mg total daily dose of glyburide. Patients who received placebo were eligible to have glyburide up-titrated

to a total daily dose of 15 mg. Up-titration of glyburide was not permitted in patients who received ONGLYZA 2.5 mg or 5 mg. Glyburide could be down-titrated in any treatment group once during the 24-week study period due to hypoglycemia as deemed necessary by the investigator. Approximately 92% of patients in the placebo plus glyburide group were up-titrated to a final total daily dose of 15 mg during the first 4 weeks of the study period. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue, added on to existing study medication. Dose titration of ONGLYZA was not permitted during the study.

In combination with glyburide, ONGLYZA 2.5 mg and 5 mg provided significant improvements in A1C, FPG, and PPG compared with the placebo plus up-titrated glyburide group (Table 7). The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 18% in the ONGLYZA 2.5 mg add-on to glyburide group, 17% in the ONGLYZA 5 mg add-on to glyburide group, and 30% in the placebo plus up-titrated glyburide group.

Table 8: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA as Add-On Combination Therapy with Glyburide*

Efficacy Parameter	**ONGLYZA 2.5 mg + Glyburide 7.5 mg N=248**	**ONGLYZA 5 mg + Glyburide 7.5 mg N=253**	**Placebo + Up-Titrated Glyburide N=267**
Hemoglobin A1C (%)	**N=246**	**N=250**	**N=264**
Baseline (mean)	8.4	8.5	8.4
Change from baseline (adjusted mean†)	−0.5	−0.6	+0.1
Difference from up-titrated glyburide (adjusted mean†)	−0.6‡	−0.7‡	
95% Confidence Interval	(−0.8, −0.5)	(−0.9, −0.6)	
Percent of patients achieving A1C <7%	22%§ (55/246)	23%§ (57/250)	9% (24/264)
Fasting Plasma Glucose (mg/dL)	**N=247**	**N=252**	**N=265**
Baseline (mean)	170	175	174
Change from baseline (adjusted mean†)	−7	−10	+1
Difference from up-titrated glyburide (adjusted mean†)	−8§	−10§	
95% Confidence Interval	(−14, −1)	(−17, −4)	
2-hour Postprandial Glucose (mg/dL)	**N=195**	**N=202**	**N=206**
Baseline (mean)	309	315	323
Change from baseline (adjusted mean†)	−31	−34	+8
Difference from up-titrated glyburide (adjusted mean†)	−38§	−42§	
95% Confidence Interval	(−50, −27)	(−53, −31)	

* Intent-to-treat population using last observation on study or last observation prior to metformin rescue therapy for patients needing rescue

† Least squares mean adjusted for baseline value

‡ p-value <0.0001 compared to placebo + up-titrated glyburide

§ p-value <0.05 compared to placebo + up-titrated glyburide

Coadministration with Metformin in Treatment-Naive Patients

A total of 1306 treatment-naive patients with type 2 diabetes mellitus participated in this 24-week, randomized, double-blind, active-controlled trial to evaluate the efficacy and safety of ONGLYZA coadministered with metformin in patients with inadequate glycemic control (A1C ≥8% to ≤12%) on diet and exercise alone. Patients were required to be treatment-naive to be enrolled in this study.

Patients who met eligibility criteria were enrolled in a single-blind, 1-week, dietary and exercise placebo lead-in period. Patients were randomized to one of four treatment arms: ONGLYZA 5 mg + metformin 500 mg, saxagliptin 10 mg + metformin 500 mg, saxagliptin 10 mg + placebo, or metformin 500 mg + placebo. The 10 mg saxagliptin dosage is not an approved dosage. ONGLYZA was dosed once daily. In the 3 treatment groups using metformin, the metformin dose was up-titrated weekly in 500 mg per day increments, as tolerated, to a maximum of 2000 mg per day based on FPG. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue as add-on therapy.

Coadministration of ONGLYZA 5 mg plus metformin provided significant improvements in A1C, FPG, and PPG compared with placebo plus metformin (Table 8).

Table 9: Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of ONGLYZA Coadministration with Metformin in Treatment-Naive Patients*

Efficacy Parameter	**ONGLYZA 5 mg + Metformin N=320**	**Placebo + Metformin N=328**
Hemoglobin A1C (%)	**N=306**	**N=313**
Baseline (mean)	9.4	9.4
Change from baseline (adjusted mean†)	−2.5	−2.0
Difference from placebo + metformin (adjusted mean†)	−0.5‡	
95% Confidence Interval	(−0.7, −0.4)	
Percent of patients achieving A1C <7%	60%§ (185/307)	41% (129/314)
Fasting Plasma Glucose (mg/dL)	**N=315**	**N=320**
Baseline (mean)	199	199
Change from baseline (adjusted mean†)	−60	−47
Difference from placebo + metformin (adjusted mean†)	−13§	
95% Confidence Interval	(−19, −6)	
2-hour Postprandial Glucose (mg/dL)	**N=146**	**N=141**
Baseline (mean)	340	355
Change from baseline (adjusted mean†)	−138	−97
Difference from placebo + metformin (adjusted mean†)	−41§	
95% Confidence Interval	(−57, −25)	

* Intent-to-treat population using last observation on study or last observation prior to pioglitazone rescue therapy for patients needing rescue

† Least squares mean adjusted for baseline value

‡ p-value <0.0001 compared to placebo + metformin
§ p-value <0.05 compared to placebo + metformin

Add-On Combination Therapy with Metformin versus Glipizide Add-On Combination Therapy with Metformin

In this 52-week, active-controlled trial, a total of 858 patients with type 2 diabetes and inadequate glycemic control (A1C >6.5% and ≤10%) on metformin alone were randomized to double-blind add-on therapy with ONGLYZA or glipizide. Patients were required to be on a stable dose of metformin (at least 1500 mg daily) for at least 8 weeks prior to enrollment.

Patients who met eligibility criteria were enrolled in a single-blind, 2-week, dietary and exercise placebo lead-in period during which patients received metformin (1500-3000 mg based on their pre-study dose). Following the lead-in period, eligible patients were randomized to 5 mg of ONGLYZA or 5 mg of glipizide in addition to their current dose of open-label metformin. Patients in the glipizide plus metformin group underwent blinded titration of the glipizide dose during the first 18 weeks of the trial up to a maximum glipizide dose of 20 mg per day. Titration was based on a goal FPG ≤110 mg/dL or the highest tolerable glipizide dose. Fifty percent (50%) of the glipizide-treated patients were titrated to the 20-mg daily dose; 21% of the glipizide-treated patients had a final daily glipizide dose of 5 mg or less. The mean final daily dose of glipizide was 15 mg.

After 52 weeks of treatment, ONGLYZA and glipizide resulted in similar mean reductions from baseline in A1C when added to metformin therapy (Table 9). This conclusion may be limited to patients with baseline A1C comparable to those in the trial (91% of patients had baseline A1C <9%).

From a baseline mean body weight of 89 kg, there was a statistically significant mean reduction of 1.1 kg in patients treated with ONGLYZA compared to a mean weight gain of 1.1 kg in patients treated with glipizide ($p<0.0001$).

Table 10: Glycemic Parameters at Week 52 in an Active-Controlled Trial of ONGLYZA versus Glipizide in Combination with Metformin*

Efficacy Parameter	**ONGLYZA 5 mg + Metformin N=428**	**Titrated Glipizide + Metformin N=430**
Hemoglobin A1C (%)	**N=423**	**N=423**
Baseline (mean)	7.7	7.6
Change from baseline (adjusted mean†)	−0.6	−0.7
Difference from glipizide + metformin (adjusted mean†)	0.1	
95% Confidence Interval	(−0.02, 0.2)‡	
Fasting Plasma Glucose (mg/dL)	**N=420**	**N=420**
Baseline (mean)	162	161
Change from baseline (adjusted mean†)	−9	−16
Difference from glipizide + metformin (adjusted mean†)	6	
95% Confidence Interval	(2, 11)§	

* Intent-to-treat population using last observation on study

† Least squares mean adjusted for baseline value

‡ ONGLYZA + metformin is considered non-inferior to glipizide + metformin because the upper limit of this confidence interval is less than the prespecified non-inferiority margin of 0.35%

§ Significance not tested

Add-On Combination Therapy with Insulin (with or without metformin)

A total of 455 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with insulin in patients with inadequate glycemic control (A1C ≥7.5% and ≤11%) on insulin alone (N=141) or on insulin in combination with a stable dose of metformin (N=314). Patients were required to be on a stable dose of insulin (≥30 units to ≤150 units daily) with ≤20% variation in total daily dose for ≥8 weeks prior to screening. Patients entered the trial on intermediate- or long-acting (basal) insulin or premixed insulin. Patients using short-acting insulins were excluded unless the short-acting insulin was administered as part of a premixed insulin.

Patients who met eligibility criteria were enrolled in a single-blind, four-week, dietary and exercise placebo lead-in period during which patients received insulin (and metformin if applicable) at their pretrial dose(s). Following the lead-in period, eligible patients were randomized to add-on therapy with either ONGLYZA 5 mg or placebo. Doses of the antidiabetic therapies were to remain stable but patients were rescued and allowed to

adjust the insulin regimen if specific glycemic goals were not met or if the investigator learned that the patient had self-increased the insulin dose by >20%. Data after rescue were excluded from the primary efficacy analyses.

Add-on therapy with ONGLYZA 5 mg provided significant improvements from baseline to Week 24 in A1C and PPG compared with add-on placebo (Table 10). Similar mean reductions in A1C versus placebo were observed for patients using ONGLYZA 5 mg add-on to insulin alone and ONGLYZA 5 mg add-on to insulin in combination with metformin (−0.4% and −0.4%, respectively). The percentage of patients who discontinued for lack of glycemic control or who were rescued was 23% in the ONGLYZA group and 32% in the placebo group.

The mean daily insulin dose at baseline was 53 units in patients treated with ONGLYZA 5 mg and 55 units in patients treated with placebo. The mean change from baseline in daily dose of insulin was 2 units for the ONGLYZA 5 mg group and 5 units for the placebo group.

Table 11: Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of ONGLYZA as Add-On Combination Therapy with Insulin*

Efficacy Parameter	**ONGLYZA 5 mg + Insulin (+/− Metformin) N=304**	**Placebo + Insulin (+/− Metformin) N=151**
Hemoglobin A1C (%)	**N=300**	**N=149**
Baseline (mean)	8.7	8.7
Change from baseline (adjusted mean†)	−0.7	−0.3
Difference from placebo (adjusted mean†)	−0.4‡	
95% Confidence Interval	(−0.6, −0.2)	
2-hour Postprandial Glucose (mg/dL)	**N=262**	**N=129**
Baseline (mean)	251	255
Change from baseline (adjusted mean†)	−27	−4
Difference from placebo (adjusted mean†)	−23§	
95% Confidence Interval	(−37, −9)	

* Intent-to-treat population using last observation on study or last observation prior to insulin rescue therapy for patients needing rescue

† Least squares mean adjusted for baseline value and metformin use at baseline

‡ p-value <0.0001 compared to placebo + insulin

§ p-value <0.05 compared to placebo + insulin

The change in fasting plasma glucose from baseline to Week 24 was also tested, but was not statistically

significant. The percent of patients achieving an A1C <7% was 17% (52/300) with ONGLYZA in combination with insulin compared to 7% (10/149) with placebo. Significance was not tested.

Add-On Combination Therapy with Metformin plus Sulfonylurea

A total of 257 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with metformin plus a sulfonylurea in patients with inadequate glycemic control (A1C ≥7% and ≤10%). Patients were to be on a stable combined dose of metformin extended-release or immediate-release (at maximum tolerated dose, with minimum dose for enrollment being 1500 mg) and a sulfonylurea (at maximum tolerated dose, with minimum dose for enrollment being ≥50% of the maximum recommended dose) for ≥8 weeks prior to enrollment.

Patients who met eligibility criteria were entered in a 2-week enrollment period to allow assessment of inclusion/exclusion criteria. Following the 2-week enrollment period, eligible patients were randomized to either double-blind ONGLYZA (5 mg once daily) or double-blind matching placebo for 24 weeks. During the 24-week double-blind treatment period, patients were to receive metformin and a sulfonylurea at the same constant dose ascertained during enrollment. Sulfonylurea dose could be down titrated once in the case of a major hypoglycemic event or recurring minor hypoglycemic events. In the absence of hypoglycemia, titration (up or down) of study medication during the treatment period was prohibited.

ONGLYZA in combination with metformin plus a sulfonylurea provided significant improvements in A1C and PPG compared with placebo in combination with metformin plus a sulfonylurea (Table 11). The percentage of patients who discontinued for lack of glycemic control was 6% in the ONGLYZA group and 5% in the placebo group.

Table 12: Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of ONGLYZA as Add-On Combination Therapy with Metformin plus Sulfonylurea*

Efficacy Parameter	**ONGLYZA 5 mg + Metformin plus Sulfonylurea N=129**	**Placebo + Metformin plus Sulfonylurea N=128**
Hemoglobin A1C (%)	**N=127**	**N=127**
Baseline (mean)	8.4	8.2
Change from baseline (adjusted mean†)	−0.7	−0.1
Difference from placebo (adjusted mean†)	−0.7‡	
95% Confidence Interval	(−0.9, −0.5)	

Table 12: Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of ONGLYZA as Add-On Combination Therapy with Metformin plus Sulfonylurea*

Efficacy Parameter	**ONGLYZA 5 mg + Metformin plus Sulfonylurea N=129**	**Placebo + Metformin plus Sulfonylurea N=128**
2-hour Postprandial Glucose (mg/dL)	**N=115**	**N=113**
Baseline (mean)	268	262
Change from baseline (adjusted mean†)	−12	5
Difference from placebo (adjusted mean†)	−17§	
95% Confidence Interval	(−32, −2)	

* Intent-to-treat population using last observation prior to discontinuation

† Least squares mean adjusted for baseline value

‡ p-value <0.0001 compared to placebo + metformin plus sulfonylurea

§ p-value <0.05 compared to placebo + metformin plus sulfonylurea

The change in fasting plasma glucose from baseline to Week 24 was also tested, but was not statistically significant. The percent of patients achieving an A1C <7% was 31% (39/127) with ONGLYZA in combination with metformin plus a sulfonylurea compared to 9% (12/127) with placebo. Significance was not tested.

Add-on Combination Therapy with Metformin plus an SGLT2 Inhibitor

A total of 315 patients with type 2 diabetes participated in this 24-week randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA added to dapagliflozin (an SGLT2 inhibitor) and metformin in patients with a baseline of HbA1c ≥7% to ≤10.5%. The mean age of these subjects was 54.6 years, 1.6% were 75 years or older and 52.7% were female. The population was 87.9% White, 6.3% Black or African American, 4.1% Asian, and 1.6% Other race. At baseline the population had diabetes for an average of 7.7 years and a mean HbA1c of 7.9%. The mean eGFR at baseline was 93.4 mL/min/1.73 m2. Patients were required to be on a stable dose of metformin (≥1500 mg per day) for at least 8 weeks prior to enrollment. Eligible subjects who completed the screening period entered the lead in treatment period, which included open-label metformin and 10 mg dapagliflozin treatment. Following the lead-in period, eligible patients were randomized to ONGLYZA 5 mg (N=153) or placebo (N =162).

The group treated with add-on ONGLYZA had statistically significant greater reductions in HbA1c from baseline versus the group treated with placebo (see Table 13).

Table 13: HbA1c Change from Baseline at Week 24 in a Placebo-Controlled Trial of ONGLYZA as Add-on to Dapagliflozin and Metformin§

	ONGLYZA 5 mg (N=153) †	Placebo (N=162) †
	In combination with Dapagliflozin and Metformin	
Hemoglobin A1C (%)*		
Baseline (mean)	8.0	7.9
Change from baseline (adjusted mean‡) 95% Confidence Interval	−0.5 (−0.6, −0.4)	−0.2 (−0.3, −0.1)
Difference from placebo (adjusted mean) 95% Confidence Interval	−0.4¶ (−0.5, −0.2)	

* Analysis of Covariance including all post-baseline data regardless of rescue or treatment discontinuation. Model estimates calculated using multiple imputation to model washout of the treatment effect using placebo data for all subjects having missing week 24 data.

† Number of randomized and treated patients.

‡ Least squares mean adjusted for baseline value.

§ There were 6.5% (n=10) of randomized subjects in the saxagliptin arm and 3.1% (n=5) in the placebo arm for whom change from baseline HbA1c data was missing at week 24. Of the subjects who discontinued study medication early, 9.1% (1 of 11) in the saxagliptin arm and 16.7% (1 of 6) in the placebo arm had HbA1c measured at week 24.

¶ p-value <0.0001

The known proportion of patients achieving HbA1c <7% at Week 24 was 35.3% in the saxagliptin treated group compared to 23.1% in the placebo treated group.

14.2 Renal Impairment

A total of 170 patients participated in a 12-week, randomized, double-blind, placebo-controlled trial conducted to evaluate the efficacy and safety of ONGLYZA 2.5 mg once daily compared with placebo in patients with type 2 diabetes and moderate (n=90) or severe (n=41) renal impairment or ESRD (n=39). In this trial, 98% of the patients were using background antidiabetic medications (75% were using insulin and 31% were using oral antidiabetic medications, mostly sulfonylureas).

After 12 weeks of treatment, ONGLYZA 2.5 mg provided significant improvement in A1C compared to placebo (Table 14). In the subgroup of patients with ESRD, ONGLYZA and placebo resulted in comparable reductions in A1C from baseline to Week 12. This finding is inconclusive because the trial was not adequately powered to show efficacy within specific subgroups of renal impairment.

After 12 weeks of treatment, the mean change in FPG was −12 mg/dL with ONGLYZA 2.5 mg and −13 mg/dL with placebo. Compared to placebo, the mean change in FPG with ONGLYZA was −12 mg/dL in the subgroup of patients with moderate renal impairment, −4 mg/dL in the subgroup of patients with severe renal impairment,

and +44 mg/dL in the subgroup of patients with ESRD. These findings are inconclusive because the trial was not adequately powered to show efficacy within specific subgroups of renal impairment.

Table 14: A1C at Week 12 in a Placebo-Controlled Trial of ONGLYZA in Patients with Renal Impairment*

Efficacy Parameter	**ONGLYZA 2.5 mg N=85**	**Placebo N=85**
Hemoglobin A1C (%)	**N=81**	**N=83**
Baseline (mean)	8.4	8.1
Change from baseline (adjusted mean†)	−0.9	−0.4
Difference from placebo (adjusted mean†)	−0.4‡	
95% Confidence Interval	(−0.7, −0.1)	

* Intent-to-treat population using last observation on study

† Least squares mean adjusted for baseline value

‡ p-value <0.01 compared to placebo

14.3 Cardiovascular Safety Trial

The cardiovascular risk of ONGLYZA was evaluated in SAVOR, a multicenter, multinational, randomized, double-blind study comparing ONGLYZA (N=8280) to placebo (N=8212), both administered in combination with standard of care, in adult patients with type 2 diabetes at high risk for atherosclerotic cardiovascular disease. Of the randomized study subjects, 97.5% completed the trial, and the median duration of follow-up was approximately 2 years. The trial was event-driven, and patients were followed until a sufficient number of events were accrued.

Subjects were at least 40 years of age, had A1C ≥6.5%, and multiple risk factors (21% of randomized subjects) for cardiovascular disease (age ≥55 years for men and ≥60 years for women plus at least one additional risk factor of dyslipidemia, hypertension, or current cigarette smoking) or established (79% of the randomized subjects) cardiovascular disease defined as a history of ischemic heart disease, peripheral vascular disease, or ischemic stroke. Overall, the use of diabetes medications was balanced across treatment groups (metformin 69%, insulin 41%, sulfonylureas 40%, and TZDs 6%). The use of cardiovascular disease medications was also balanced (angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs] 79%, statins 78%, aspirin 75%, beta blockers 62%, and non aspirin antiplatelet medications 24%).

The majority of subjects were male (67%) and Caucasian (75%) with a mean age of 65 years. Approximately 16% of the population had moderate (estimated glomerular filtration rate [eGFR] ≥30 to ≤50 mL/min) to severe (eGFR <30 mL/min) renal impairment, and 13% had a prior history of heart failure. Subjects had a median duration of type 2 diabetes mellitus of approximately 10 years, and a mean baseline A1C level of 8.0%. Approximately 5% of subjects were treated with diet and exercise only at baseline. Overall, the use of diabetes medications was balanced across treatment groups (metformin 69%, insulin 41%, sulfonylureas 40%, and TZDs

6%). The use of cardiovascular disease medications was also balanced (ACE inhibitors or ARBs 79%, statins 78%, aspirin 75%, beta-blockers 62%, and non-aspirin antiplatelet medications 24%).

The primary analysis in SAVOR was time to first occurrence of a Major Adverse Cardiac Event (MACE). A major adverse cardiac event in SAVOR was defined as a cardiovascular death or a nonfatal myocardial infarction (MI) or a nonfatal ischemic stroke. The study was designed as a non-inferiority trial with a pre-specified risk margin of 1.3 for the hazard ratio of MACE and was also powered for a superiority comparison if non-inferiority was demonstrated.

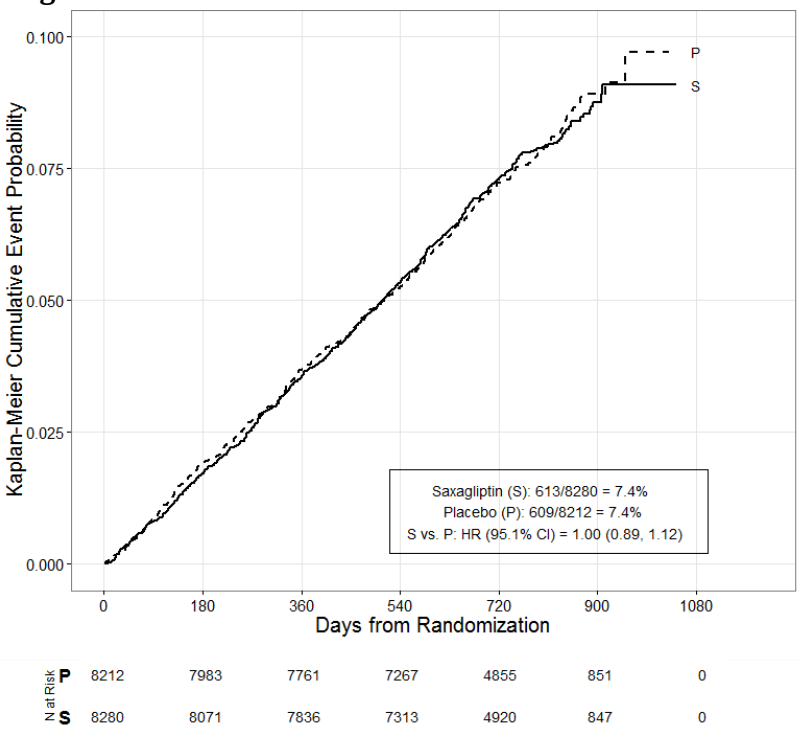
The results of SAVOR, including the contribution of each component to the primary composite endpoint, are shown in Table 15. The incidence rate of MACE was similar in both treatment arms: 3.8 MACE per 100 patient-years on placebo vs. 3.8 MACE per 100 patient-years on ONGLYZA. The estimated hazard ratio of MACE associated with ONGLYZA relative to placebo was 1.00 with a 95.1% confidence interval of (0.89, 1.12). The upper bound of this confidence interval, 1.12, excluded a risk margin larger than 1.3.

Table 15: Major Adverse Cardiovascular Events (MACE) by Treatment Group in the SAVOR Trial

	ONGLYZA		**Placebo**		**Hazard Ratio**
	Number of Subjects (%)	**Rate per 100 PY**	**Number of Subjects (%)**	**Rate per 100 PY**	**(95.1% CI)**
Composite of first event of CV death, non-fatal MI or non-fatal ischemic stroke (MACE)	**N=8280**	**Total PY = 16308.8**	**N=8212**	**Total PY = 16156.0**	
	613 (7.4)	3.8	609 (7.4)	3.8	1.00 (0.89, 1.12)
CV death	245 (3.0)	1.5	234 (2.8)	1.4	
Non-fatal MI	233 (2.8)	1.4	260 (3.2)	1.6	
Non-fatal ischemic stroke	135 (1.6)	0.8	115 (1.4)	0.7	

The Kaplan-Meier-based cumulative event probability is presented in Figure 2 for time to first occurrence of the primary MACE composite endpoint by treatment arm. The curves for both ONGLYZA and placebo arms are close together throughout the duration of the trial. The estimated cumulative event probability is approximately linear for both arms, indicating that the incidence of MACE for both arms was constant over the trial duration.

Figure 2: Cumulative Percent of Time to First MACE



Vital status was obtained for 99% of subjects in the trial. There were 798 deaths in the SAVOR trial. Numerically more patients (5.1%) died in the ONGLYZA group than in the placebo group (4.6%). The risk of deaths from all cause (Table 16) was not statistically different between the treatment groups (HR: 1.11; 95.1% CI: 0.96, 1.27).

Table 16: All-cause mortality by Treatment Group in the SAVOR Study

	ONGLYZA		Placebo		Hazard Ratio
	Number of Subjects (%)	**Rate per 100 PY**	**Number of Subjects (%)**	**Rate per 100 PY**	**(95.1% CI)**
	N=8280	**PY=16645.3**	**N=8212**	**PY=16531.5**	
All-cause mortality	420 (5.1)	2.5	378 (4.6)	2.3	1.11 (0.96, 1.27)
CV death	269 (3.2)	1.6	260 (3.2)	1.6	
Non-CV death	151 (1.8)	0.9	118 (1.4)	0.7	

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ONGLYZA® (saxagliptin) tablets have markings on both sides and are available in the strengths and packages listed in Table 17.

Table 17: ONGLYZA Tablet Presentations

Tablet Strength	Film-Coated Tablet Color/Shape	Tablet Markings	Pack Type
5 mg	pink biconvex, round	"5" on one side and "4215" on the reverse, in blue ink	Alu/Alu blisters
2.5 mg	pale yellow to light yellow biconvex, round	"2.5" on one side and "4214" on the reverse, in blue ink	Alu/Alu blisters

Pack size

See pack size on outer cardboard box.

Storage and Handling

Store below 30°C.

Shelf-life

Please refer to expiry date on the blister strip or outer carton.

Manufactured by:

AstraZeneca Pharmaceuticals LP

4601 Highway 62 East, Mount Vernon, Indiana 47620, USA

Packaged by:

AstraZeneca UK Limited

Silk Road Business Park, Macclesfield, Cheshire, SK10 2NA, United Kingdom.

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