**SUPPLEMENTARY MATERIAL**

**Fig. S1.** PF-06751979 mean plasma concentration–time curves after single and multiple doses in studies B8271001 and B8271004.


HA, healthy adults; HOS, healthy older subjects; QD, once daily.

**Fig. S2.** Predicted distribution of individual PD responses when PF-06751979 is administered at 30 mg QD, 75 mg QD, and 110 mg QD.

****PD, pharmacodynamics; QD, once daily.

**Table S1**. Mean placebo-adjusted percent change from baseline (2-sided 80% CI) in plasma Aβ fragments in healthy adults treated with single- and multiple-ascending doses of PF-06751979 in studies B8271001 and B8271004

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| **Part A: PF-06751979 single-ascending dose in healthy adults****Mean placebo-adjusted percent change from baseline (2-sided 80% CI)** |
| **PF-06751979 dose** |
| Plasma fragment | Timepost-dose(hours) | 3 mg(N = 5) | 12 mg(N = 6) | 40 mg(N = 6) | 160 mg(N = 6) | 200 mg(N = 6) | 400 mg(N = 6) | 540 mg (N = 6) | 200 mg fed(N = 6) |
| Aβ1-40 | 4 | –41.1(–47.00, –34.62) | –57.5(–61.62, –52.85) | –52.9(–57.57, –47.79) | –61.6(–65.44, –57.45) | – | – | – | – |
|  | 6 | – | – | – | – | –84.3(–86.68, –81.52) | –78.2(–81.53, –74.33) | –86.9(–88.90, –84.57) | –77.1(–80.54, –72.94) |
|  | 8 | –50.5(–56.30, –44.05) | –67.0(–70.76, –62.83) | –69.0(–72.50, –64.99) | –80.9(–83.08, –78.45) | –87.7(–89.16, –85.94) | –82.4(–84.52, –79.88) | –89.0(–90.36, –7.47) | –80.7(–83.07, –78.01) |
|  | 24 | –34.8(–41.51, –27.41) | –61.0(–64.91, –56.65) | –66.6(–69.98, –62.85) | –84.0(–85.63, –82.21) | –90.2(–91.00, –89.35) | –84.9(–86.13, –83.54) | –89.4(–90.27,– 88.44) | –83.5(–84.87, –82.00) |
|  | 48 | –28.0(–35.50, –19.63) | –53.3(–58.07, –48.02) | –57.4(–61.76, –52.51) | –82.0(–83.88, –79.98) | –90.2(–91.11, –89.23) | –86.1(–87.41, –84.71) | –90.3(–91.17, –89.25) | –84.3(–85.79, –82.70) |
| Aβx-40 | 4 | –34.1(–39.27, –28.55) | –48.4(–52.41, –44.12) | –39.6(–44.26, –34.61) | –45.4 (–49.64, –40.89) | – | – | – | – |
|  | 6 | – | – | – | – | –65.1(–68.23, –61.72) | –58.3(–61.99, –54.27) | –63.3(–66.59, –59.67) | –59.4(–62.98, –55.41) |
|  | 8 | –39.8(–44.23, –35.01) | –53.3(–56.72, –49.62) | –51.6(–55.08, –47.75) | –58.2(–61.21, –54.85) | –66.9(–69.85, –63.59) | –63.1(–66.37, –59.45) | –68.3(–71.19, –65.14) | –62.0(–65.41, –58.24) |
|  | 24 | –25.1(–31.97, –17.46) | –49.2(–53.8, –44.2) | –46.6(–51.39, –41.34) | –60.8(–64.32, –56.92) | –69.7(–72.21, –66.85) | –67.4(–70.12, –64.40) | –72.2(–74.60, –69.63) | –62.9(–66.05, –59.50) |
|  | 48 | –18.0(–25.44, –9.88) | –40.0(–45.26, –34.13) | –38.8(–44.18, –32.88) | –56.5(–60.33, –52.28) | –70.0(–72.76, –66.98) | –67.0(–69.99, –63.66) | –72.9(–75.45, –70.18) | –62.4(–65.84, –58.60) |
| Aβ total | 4 | –29.8(–35.01, –24.10) | –45.0(–48.92, –40.73) | –36.8(–41.46, –31.82) | –45.8(–49.89, –41.46) | – | – | – | – |
|  | 6 | – | – | – | – | –51.8(–59.59, –42.42) | –59.3(–66.42, –50.67) | –57.6(–64.49, –49.29) | –49.1(–57.44, –39.23) |
|  | 8 | –36.4(–42.06, –30.19) | –46.9(–51.37, –41.92) | –47.8(–52.35, –42.90) | –57.4(–61.11, –53.29) | –59.1(–65.70, –51.29) | –60.9(–67.71, –52.72) | –66.8(–72.19, –60.43) | –56.4(–63.49, –48.05) |
|  | 24 | –27.7(–36.81, –17.25) | –43.9(–50.64, –36.21) | –49.1(–55.30, –42.12) | –60.8(–65.62, –55.40) | –64.2(–70.68, –56.37) | –58.2(–66.22, –48.36) | –69.4(–74.94, –62.64) | –58.4(–65.93, –49.21) |
|  | 48 | –19.0(–26.33, –10.93) | –35.4(–40.98, –29.26) | –33.0 (–38.87, –26.50) | –53.8(–57.94, –49.31) | –62.0(–68.40, –54.38) | –67.4(–73.25, –60.24) | –65.2(–71.09, –58.19) | –59.6(–66.40, –51.41) |

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| **Part B: PF-06751979 multiple-ascending dose in healthy adults****Mean placebo-adjusted percent change from baseline (2-sided 80% CI)** |
| **PF-06751979 dose** |
| Plasma fragment | Day | 5 mg(N = 8) | 15 mg(N = 8) | 50 mg(N = 8) | 125 mg(N = 12) | 275 mg(N = 9) |
| Aβ1-40 | 1 | – | – | – | –87.7(–88.27, –87.11) | –88.3(–88.87, –87.69) |
|  | 2 | –45.2(–49.54, –40.42) | –58.0(–61.46, –54.23) | –83.7(–84.98, –82.26) | – | – |
|  | 4 | –53.7(–57.43, –49.74) | –67.1(–69.77, –64.10) | –87.0(–88.00, –85.83) | –87.4(–87.84, –86.88) | –87.3(–87.80, –86.79) |
|  | 7 | –58.2 (–61.54, –54.60) | –71.4(–73.80, –68.89) | –87.1(–88.10, –85.94) | –87.1(–87.59, –86.63) | –87.1(–87.55, –86.53) |
|  | 10 | –58.0 (–61.38, –54.40) | –68.9(–71.43, –66.07) | –87.2(–88.20, –86.07) | –86.8(–87.07, –86.61) | –86.8(–87.02, –86.53) |
|  | 14 | –58.7(–61.95, –55.08) | –68.0(–70.66, –65.16) | –86.2(–87.26, –84.95) | –87.5(–87.79, –87.14) | –87.4(–87.75, –87.06) |
| Aβx-40 | 1 | – | – | – | –69.1(–71.37, –66.57) | –70.4(–72.73, –67.83) |
|  | 2 | –33.7(–38.36, –28.77) | –43.9(–47.87, –39.72) | –58.5(–61.37, –55.37) | – | – |
|  | 4 | –40.5(–44.66, –36.06) | –50.4(–53.83, –46.61) | –63.5(–66.07, –60.80) | –72.3(–74.51, –69.82) | –73.8(–76.02, –71.30) |
|  | 7 | –41.1(–45.19, –36.67) | –56.5(–59.58, –53.26) | –61.9(–64.55, –59.04) | –71.0(–74.16, –67.49) | –72.2(–75.44, –68.64) |
|  | 10 | –41.7(–45.79, –37.36) | –50.9(–54.31, –47.17) | –62.3(–64.93, –59.48) | –70.8(–73.51, –67.80) | –74.1(–76.63, –71.24) |
|  | 14 | –40.6(–44.70, –36.10) | –51.4(–54.78, –47.70) | –59.6(–62.40, –56.56) | –71.7(–74.18, –68.92) | –71.8(–74.48, –68.91) |
| Aβ total | 1 | – | – | – | –59.6(–67.75, –49.32) | –64.0(–71.53, –54.54) |
|  | 2 | –29.33(–38.00, 19.45) | –40.3(–47.58, –32.00) | –56.8(–62.16, –50.75) | – | – |
|  | 4 | –35.4(–43.33, –26.37) | –45.8(–52.44, –38.31) | –61.6(–66.36, –56.22) | –58.1(–68.12, –44.94) | –65.8(–74.27, –54.50) |
|  | 7 | –35.6(–43.48, –26.57) | –52.2(–58.02, –45.55) | –63.0(–67.55, –57.77) | –62.8(–70.73, –52.72) | –67.3(–74.50, –58.06) |
|  | 10 | –31.9(–40.24, –22.36) | –48.7(–54.94, –41.55) | –65.3(–69.62, –60.47) | –62.1(–71.31, –49.98) | –70.4(–77.83, –60.40) |
|  | 14 | –37.4(–45.06, –28.62) | –45.0(–51.72, –37.38) | –61.8(–66.51, –56.42) | –59.1(–68.51, –46.80) | –69.0(–76.40, –59.25) |

Aβ, amyloid-beta; CI, confidence interval.