# Development of Canagliflozin: Mechanistic Absorption Modeling During Late-Stage Formulation and Process Optimization

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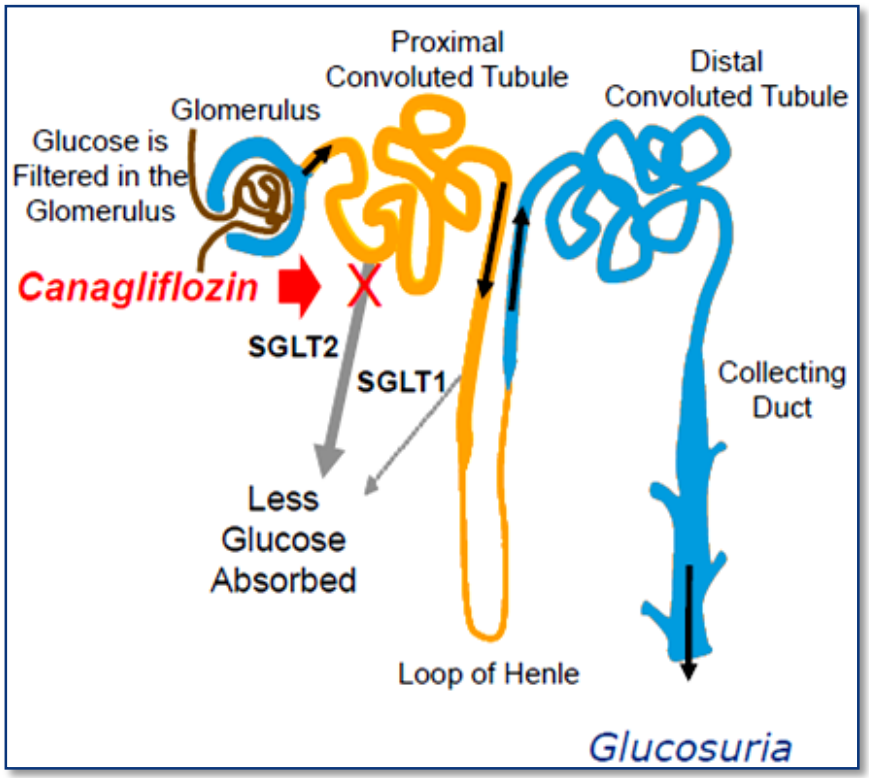
# Canagliflozin

- An orally active renal SGLT2 inhibitor approved as an adjunct to diet and exercise to improve the glycemic control in adults with T2DM
- **Doses:** 100/300 mg once daily, before the first meal of the day
- **Mechanism of Action:**
  - Inhibits SGLT2 activity
  - Decreases renal glucose reabsorption
  - Increases UGE thereby reducing PG
  - Increases insulin sensitivity & decreases gluconeogenesis
  - Reduces body weight (~300-400 kcal/day)
  - Improves β-cell function




PG: plasma glucose; SGLT2: sodium glucose co-transporter 2; T2DM: type 2 diabetes mellitus; UGE: urinary glucose excretion

# Pharmacokinetics of Canagliflozin

- Similar PK profile in healthy adults vs. patients with T2DM
- Time to attain peak plasma concentrations: ~1–2 hours after dosing
- Glucuronidated mainly by UGT1A9 and UGT2B4 to 2 inactive O-glucuronide metabolites
- No food effect
- Mean absolute oral bioavailability: 65%
- Elimination half-life: ~10 - 13 hours
- Biopharmaceutics Classification System class 4 compound (low solubility and permeability)

PK: pharmacokinetics; UGT: uridine diphosphate glucuronosyltransferase; T2DM: type 2 diabetes mellitus

# Formulation Development

- In-line milling step was added to the crystallization process to
  - reduce the coarse particles
  - narrow the particle size distribution (PE)

- PE API was used for drug product resupply (later parts of Phase 3 studies)

- The formulation compositions of both NPE and PE API were identical

API: active pharmaceutical ingredient; NPE: non-particle-engineered; PE: particle-engineered

# Various Particle Size Used in Clinical Studies

| NPE API Lot Number | $d_{10}$ (µm) | $d_{50}$ (µm) | $d_{90}$ (µm) |
|---|---|---|---|
| NPE Lot 1 | 20 | 63 | 173 |
| NPE Lot 2 | 8 | 179 | 512 |
| NPE Lot 3 | 15 | 49 | 142 |
| NPE Lot 4 | 31 | 86 | 348 |
| NPE Lot 5 | 26 | 78 | 276 |
| NPE Lot 6 | 9 | 29 | 101 |
| NPE Lot 7 | 11 | 35 | 114 |
| NPE Lot 8 | 12 | 37 | 124 |
| NPE Lot 9 | 10 | 36 | 119 |
| NPE Lot 10 | 13 | 45 | 138 |
| NPE Lot 11 | 11 | 35 | 99 |

| PE API Lot Number | $d_{10}$ (µm) | $d_{50}$ (µm) | $d_{90}$ (µm) |
|---|---|---|---|
| PE Lot 1 | 16 | 40 | 88 |
| PE Lot 2 | 20 | 49 | 102 |
| PE Lot 3 | 22 | 53 | 108 |
| PE Lot 4 | 19 | 39 | 71 |
| PE Lot 5 | 17 | 35 | 67 |
| PE Lot 6 | 23 | 48 | 93 |
| PE Lot 7 | 21 | 44 | 87 |
| PE Lot 8 | 21 | 45 | 90 |
| PE Lot 9 | 24 | 50 | 94 |
| PE Lot 10 | 21 | 45 | 89 |
| PE Lot 11 | 19 | 42 | 88 |
| PE Lot 12 | 22 | 47 | 95 |

API: active pharmaceutical ingredient; d10, d50, and d90: diameter for which 10%, 50%, and 90% (respectively) by volume of the particles are less than this value; NPE: non-particle-engineered; PE: particle-engineered

# Percentage of Patients: NPE vs. PE in Phase 3 Studies

| Phase 3 Study | NPE[a] | | PE[a] | | Both[a] | |
|---|---|---|---|---|---|---|
| | 100 mg % of patients[b] | 300 mg % of patients[b] | 100 mg % of patients[b] | 300 mg % of patients[b] | 100 mg % of patients[b] | 300 mg % of patients[b] |
| **Study 1** | 95.6, 97.3 | 47.2, 8.6 | 4.4, 1.4 | 51.7, 90.1 | 0, 1.4 | 1.1, 1.2 |
| **Study 2** | 50.3, 0 | 49.1, 0 | 15.2, 100 | 48.3, 100 | 34.4, 0 | 2.6, 0 |
| **Study 3** | 37.7, 0 | 39.6, 0 | 62.1, 100 | 60.4, 100 | 0.2, 0 | 0 |
| **Study 4** | 0 | 63.2, 1.2 | 74.3, 98.9 | 36.0, 98.8 | 25.7, 1.1 | 0.9, 0 |

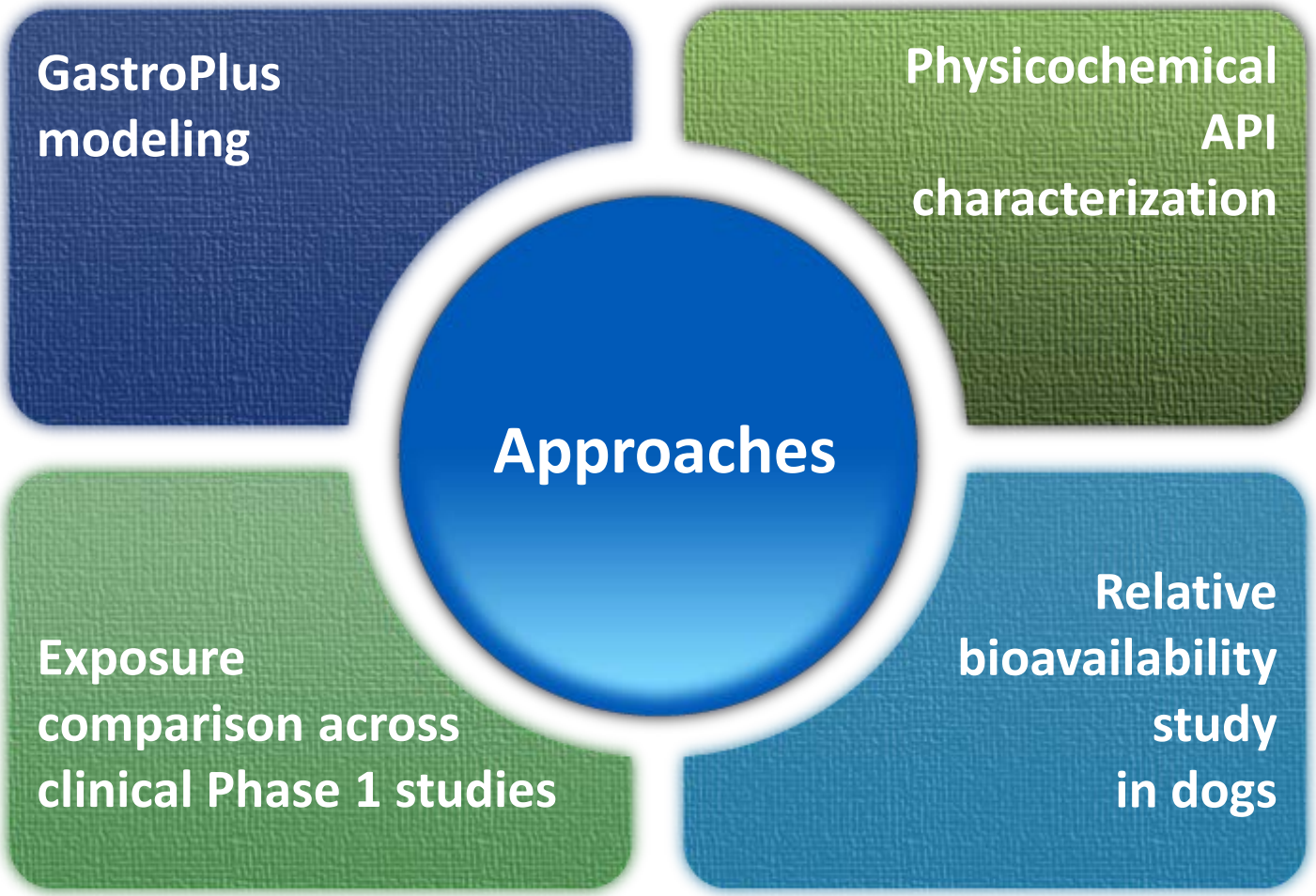
- Particle size distribution of both NPE and PE API lots used were similar
- The formulation composition of both NPE and PE API formulations was identical

NPE: non-particle-engineered; PE: particle-engineered

[a]NPE: patients received drug supply with tablets manufactured using NPE drug substance; PE: patients received drug supply with tablets manufactured using PE drug substance; Both: patients received drug supply with both types of formulations (NPE and PE)

[b]Percentages calculated with the number of patients per time interval as denominator; (percentage at randomization, percentage at time of primary endpoint)

# Approaches Taken To Access The Effect of Particle Size




API: active pharmaceutical ingredient

# GastroPlus Simulations for Canagliflozin

## Objectives

- Determine the absorption/PK model for canagliflozin
- Compare regional % absorption and gut lumen concentration-time profiles between the tablets manufactured with NPE API and with PE API
- Assess the effect of API particle size on canagliflozin exposure for immediate release formulation
- Evaluate predicted bioequivalence of the tablets manufactured with PE API vs. NPE API

**Simulations were performed using GastroPlus™ 7.0 software (Simulations Plus, Inc., Lancaster, California)**

API: active pharmaceutical ingredient; NPE: non-particle-engineered; PE: particle-engineered; PK: pharmacokinetics

# Physiologically Based Modeling and Simulations

## Methodology

**Biopharmaceutical property setup**
Imported molecular structure, in vitro data (diffusion coefficient, solubility, permeability, blood/plasma concentration ratio, plasma protein binding)

**Formulation setup**
Dosage form selection (fasted versus fed), dose volume, particle size distribution

**Physiological setup**
Gastrointestinal physiology for nine mathematical compartments of the gastrointestinal tract - using 'Human-physiological-fasted' and 'Human-physiological-fed' model

**Compartmental PK**
Data describing in vivo absorption; consists of one-, two-, or three-compartmental pharmacokinetic simulations of Cp vs. time

**PK of canagliflozin**
Across 3 dose levels (50, 100, and 300 mg)

Cp: plasma concentration; PK: pharmacokinetics

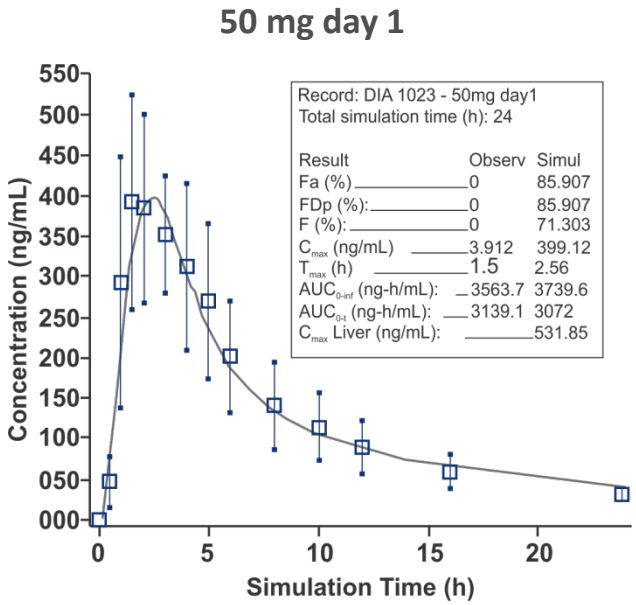
# Key physicochemical and biopharmaceutical parameters for canagliflozin used

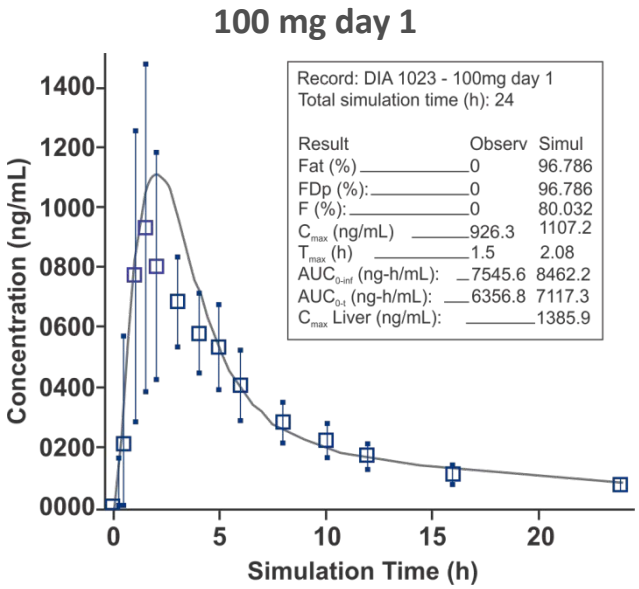
| Property | Value | References |
|---|---|---|
| logP | 3.8 | Reported by Janssen R & D |
| Diffusion coefficient | 0.67 * 10-5 $cm/s^2$ | ADMET Predictor 5.0 |
| Association constant (pKa) | None (neutral molecule) | |
| Aqueous solubility | 0.034 mg/mL @ pH 7.5 | Reported by Janssen R & D |
| FaSSIF solubility | 0.54 mg/mL @ pH 6.5 | Reported by Janssen R & D |
| FeSSIF solubility | 5.01 mg/mL @ pH 5.0 | Reported by Janssen R & D |
| Human effective permeability ($P_{eff}$) | 3.66 * 10-4 cm/s | ADMET Predictor 5.0 |
| Drug particle density | 1.2 g/mL | Default |
| Mean precipitation time | 900 s | Default |
| Blood: plasma concentration ratio ($R_{bp}$) | 0.77 | ADMET Predictor 5.0 |
| Plasma protein binding ($f_{up}$) | 2.7% unbound | Reported by Janssen R & D |

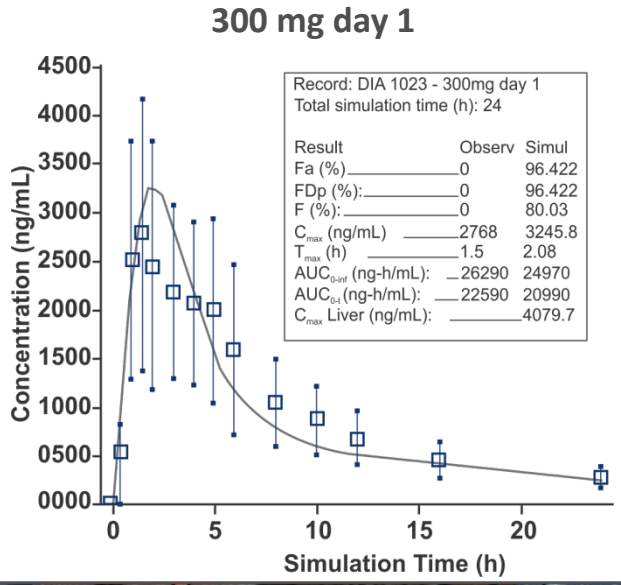
ADMET: Absorption, Distribution, Metabolism, Excretion, and Toxicity; FaSSIF: fasted state simulated intestinal fluid; FeSSIF: fed state simulated intestinal fluid

# Model Validation

## Simulated (lines) and experimental (points)



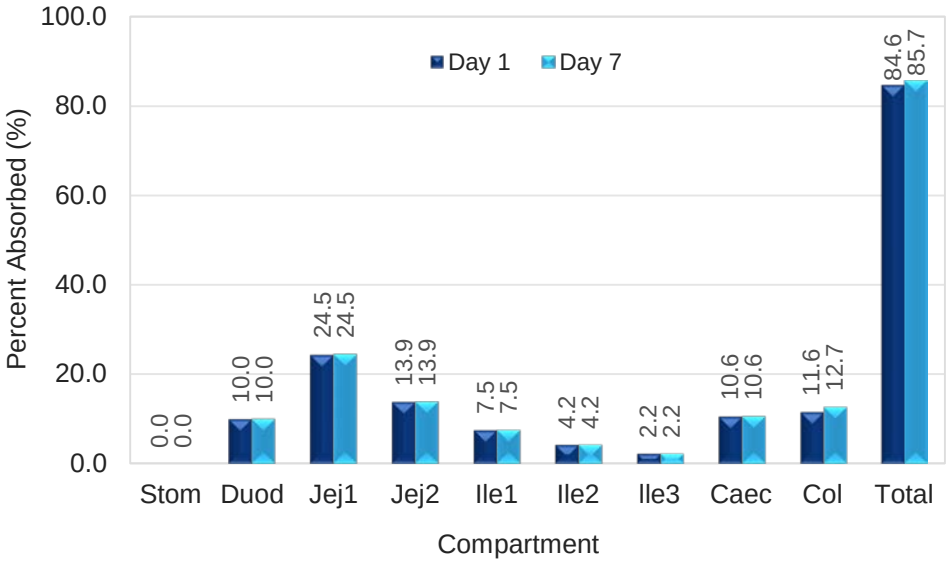




Excellent match between the measured and predicted Cp time profiles for 50, 100, and 300 mg doses

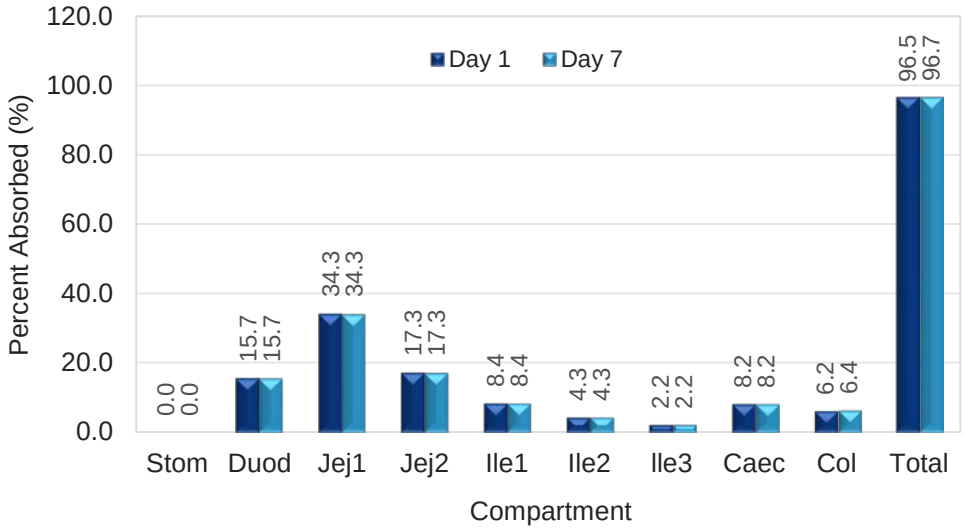
Cp-time: plasma concentration time

# Regional Absorption of once-daily Canagliflozin (300 mg)




NPE Lot

PE Lot



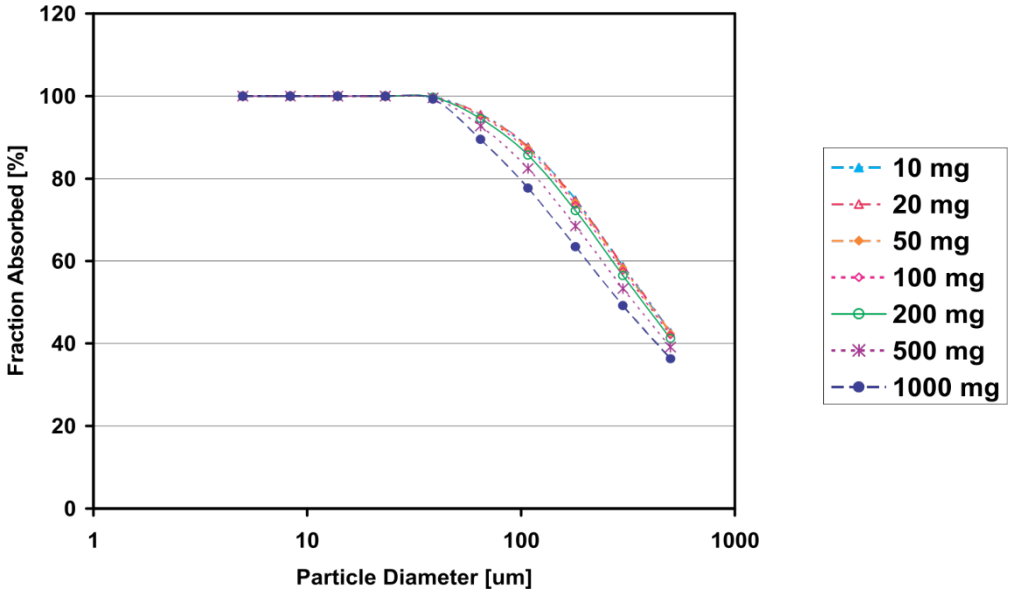

NPE: non-particle-engineered; PE: particle-engineered
Stom: stomach; Duod: Duodenum; Jej: Jejunum1; Jej: Jejunum2; Ile: Ileum1; Ile: Ileum2; Ile: Ileum3; Caec: Caecum; Col: Colon

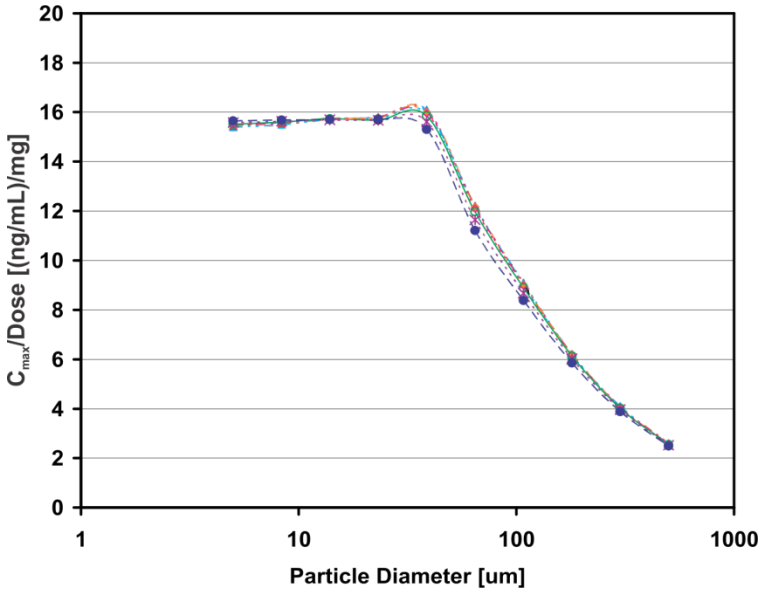
# Parameter Sensitivity Analysis

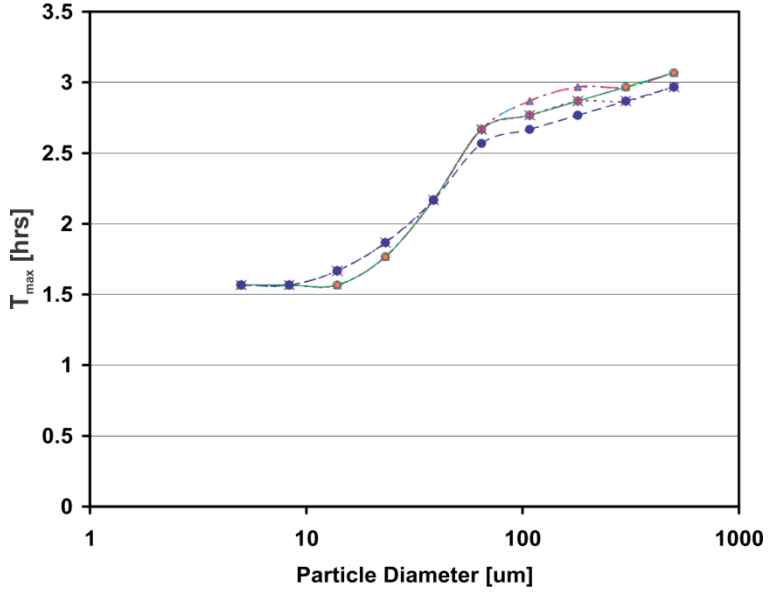
- Performed for:
  - Mean particle size
  - Particle shape factor (1/aspect ratio)
  - Particle size standard deviation
- Range of values evaluated:
  - Mean particle size: 5 – 500 µm
  - Particle shape factor: 0.835 – 3.34
  - Particle size standard deviation
- Dose range: 10 mg to 1000 mg

# Parameter Sensitivity Analysis

## Change in Fa%, $C_{max}$, $T_{max}$ as a function of mean particle diameter



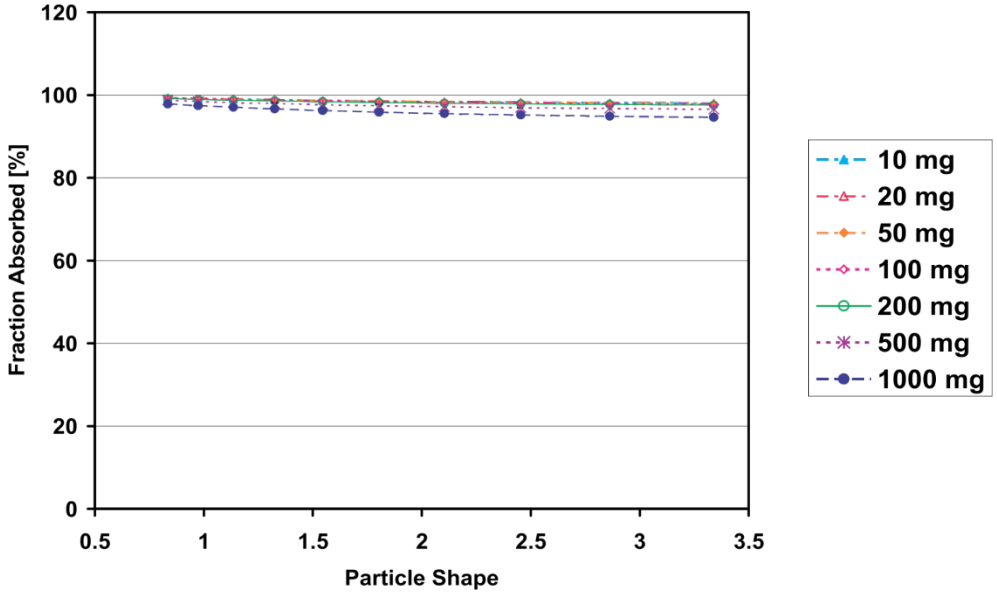



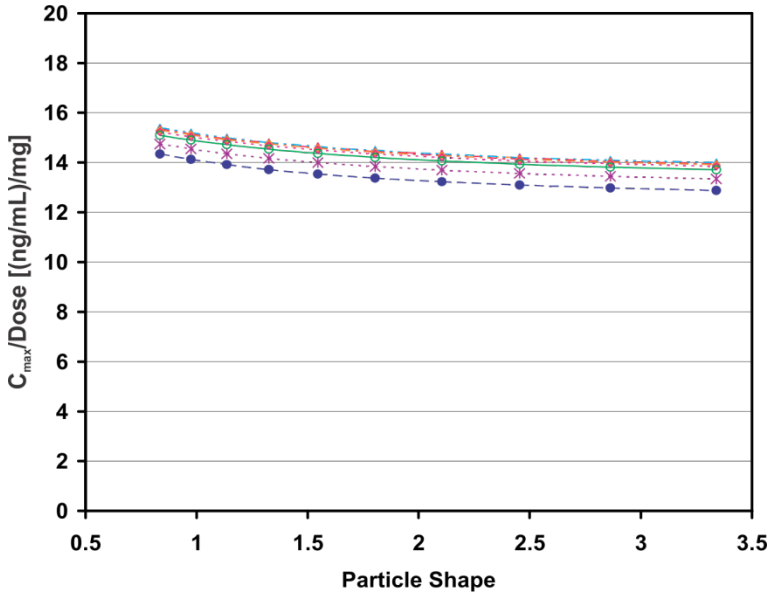



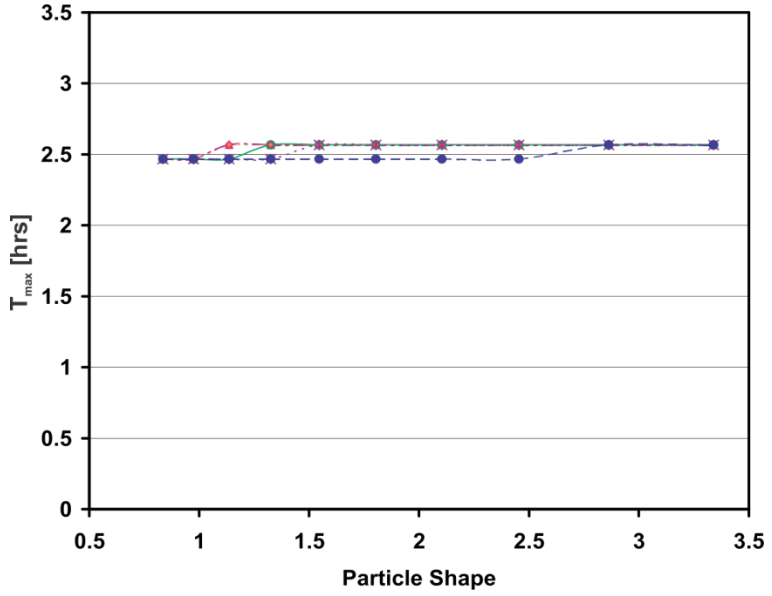

$C_{max}$: maximum observed plasma concentration; Fa%: fraction absorbed;
$T_{max}$: time to reach $C_{max}$

# Parameter Sensitivity Analysis

## Change in Fa%, $C_{max}$, $T_{max}$ as a function of particle shape




$C_{max}$: maximum observed plasma concentration; Fa%: fraction absorbed;
$T_{max}$: time to reach $C_{max}$

# Parameter Sensitivity Analysis: Conclusion

- No difference in Fa% for mean particle diameters < 70 μm
- Once the mean particle diameter exceeded 70 μm, Fa% decreased with increase in mean particle diameter
- Similar trends were seen across all doses for $C_{max}$, while, $T_{max}$ increased with increase in mean particle diameter
- Insignificant changes in Fa% across the shape factor range analyzed and only moderate changes for particle standard deviation were observed
- For the shape factor, similar trends were seen across all doses for $C_{max}$ and $T_{max}$
- Similar trends were observed across all investigated doses (10 to 1000 mg)
- The doses above 200 mg showed a slightly lower Fa%
- Analysis showed that mean particle size would be the main property that determine bioequivalence of formulation, regardless of dose

$C_{max}$: maximum observed plasma concentration; Fa%: fraction absorbed; $T_{max}$: time to reach $C_{max}$

# Virtual Bioequivalence Study Simulations

- Using crossover virtual trial simulation comparing different PSD (PK parameters: $C_{max}$ and AUC)

| API Lot | NPE or PE | d10 (µm) | d50 (µm) | d90 (µm) |
|---|---|---|---|---|
| Lot 1 | NPE | 26 | 78 | 276 |
| Lot 2 | NPE | 11 | 35 | 99 |
| Lot 3 | NPE | 14 | 43 | 116 |
| Lot 4 | NPE | 11 | 32 | 91 |
| Lot 5 | PE | 17 | 41 | 88 |

API: active pharmaceutical ingredient; $AUC_{\infty}$: area under the plasma concentration-time curve; $C_{max}$: maximum observed plasma concentration; d10, d50, and d90: diameter for which 10%, 50%, and 90% (respectively) by volume of the particles are less than this value; NPE: non-particle-engineered; PE: particle-engineered; PK: pharmacokinetics

# Virtual Bioequivalence Study Simulations

| API Lot | NPE/PE | Dose (mg) | $AUC_{\infty}$ (ng.h/mL) (N=25) | | $C_{max}$ (ng/mL) (N=25) | |
|---|---|---|---|---|---|---|
| | | | GM | GMR (90% CI) | GM | GMR (90% CI) |
| **Lot 5** | PE | 50 | 4103 | 113.9 (105.3, 123.2) | 554 | 140.2 (129.5, 151.8) |
| **Lot 1** | NPE | 50 | 3602 | | 395 | |
| **Lot 5** | PE | 100 | 7867 | 99.2 (91.9, 107.0) | 1044 | 102.5 (95.0, 110.6) |
| **Lot 3** | NPE | 100 | 7924 | | 1019 | |
| **Lot 5** | PE | 300 | 24240 | 105.6 (98.5, 113.2) | 3104 | 103.3 (96.3, 110.9) |
| **Lot 2** | NPE | 300 | 22958 | | 3004 | |
| **Lot 5** | PE | 100 | 7867 | 95.5 (90.6, 100.7) | 1044 | 92.5 (87.6, 97.6) |
| **Lot 4** | NPE | 100 | 8235 | | 1130 | |
| **Lot 5** | PE | 300 | 24240 | 101.7 (95.5, 108.3) | 3104 | 98.1 (92.0, 104.5) |
| **Lot 4** | NPE | 300 | 23835 | | 3165 | |

API: active pharmaceutical ingredient; $AUC_{\infty}$: area under the plasma concentration-time curve from time 0 to infinite time; CI: confidence interval; $C_{max}$: maximum observed plasma concentration; GM: geometric mean; GMR: geometric mean ratio; NPE: non-particle-engineered; PE: particle-engineered

# Virtual Bioequivalence Study Simulations

| API Lot | NPE/PE | Dose (mg) | $AUC_{\infty}$ (ng.h/mL) (N=250) | | $C_{max}$ (ng/mL) (N=250) | |
|---|---|---|---|---|---|---|
| | | | GM | GMR (90% CI) | GM | GMR (90% CI) |
| **Lot 5** | PE | 50 | 4180 | 113.3 (110.7, 116.1) | 551 | 139.3 (136.0, 142.7) |
| **Lot 1** | NPE | 50 | 3688 | | 395 | |
| **Lot 5** | PE | 100 | 8242 | 103.0 (100.9, 105.1) | 551 | 106.4 (104.3, 108.6) |
| **Lot 3** | NPE | 100 | 8001 | | 395 | |
| **Lot 5** | PE | 300 | 24998 | 102.2 (99.8, 104.6) | 3118 | 100.0 (97.7, 102.4) |
| **Lot 2** | NPE | 300 | 24460 | | 3117 | |
| **Lot 5** | PE | 100 | 8242 | 98.2 (96.2, 100.2) | 1068 | 95.1 (93.2, 97.0) |
| **Lot 4** | NPE | 100 | 8395 | | 1123 | |
| **Lot 5** | PE | 300 | 24998 | 101.9 (99.8, 104.1) | 3118 | 98.3 (96.3, 100.4) |
| **Lot 4** | NPE | 300 | 24525 | | 3171 | |

API: active pharmaceutical ingredient; $AUC_{\infty}$: area under the plasma concentration-time curve from time 0 to infinite time; CI: confidence interval; $C_{max}$: maximum observed plasma concentration; GM: geometric mean; GMR: geometric mean ration; NPE: non-particle-engineered; PE: particle-engineered

# Virtual Bioequivalence Study Simulations: Conclusions

- For a sufficiently powered study, the population-derived $C_{max}$ and AUC values would be bioequivalent between the tablets manufactured with NPE API (Lots 2 and 4) and tablets manufactured with PE API, regardless of the dose

- Lot 1 with larger particle size and large proportion of coarse particles is not bioequivalent for $C_{max}$ compared to PE API lots, but bioequivalent for AUC

API: active pharmaceutical ingredient; AUC: area under the plasma concentration-time curve; $C_{max}$: maximum observed plasma concentration; NPE: non-particle-engineered; PE: particle-engineered

# Other Approaches Used for Canagliflozin

# Physicochemical API Characterization

**NPE and PE API particles comparable in physical and chemical attributes**

- Comparable results  with XRD, TGA, DSC, FT-IR , FT-Raman and intrinsic dissolution
- Similar crystalline quality between the NPE and PE batches
- Fairly similar particle size distribution between NPE and PE API lots
- PE process to be more reproducible with regard to particle size distribution
- In vitro dissolution of tablets (QC dissolution) with NPE API vs. PE API was similar

API: active pharmaceutical ingredient; DSC: differential scanning calorimetry; FT-IR: Fourier transform infrared spectroscopy; FT-Raman: Fourier transform Raman spectroscopy; NPE: non-particle-engineered; PE: particle-engineered; PK: pharmacokinetics; QC: quality control; TGA: thermal gravimetric analysis; XRD: x-ray diffraction analysis

# Pooled Phase I Analysis Approach

| Parameter | Geometric Mean | | | | GMR (90% CI) |
|---|---|---|---|---|---|
| | N | PE API (Test) | N | NPE API (Reference) | |
| Single-Dose Administration | | | | | |
| $C_{max}$, (ng/mL)/mg | 156 | 9.76 | 189 | 8.52 | 114.57 (107.91; 121.64) |
| $AUC_{\infty}$, (ng.h/mL)/mg | 149 | 70.3 | 106 | 75.6 | 92.95 (87.00; 99.31) |
| Multiple-Dose Administration | | | | | |
| $C_{max}$, (ng/mL)/mg | 136 | 10.1 | 113 | 10.8 | 94.09 (87.49; 101.19) |
| $AUC_{24h}$, (ng.h/mL)/mg | 136 | 70.1 | 113 | 75.0 | 93.47 (87.40; 99.97) |

No significant effect of particle size distribution on the PK of canagliflozin was observed following administration of tablets manufactured from NPE or PE API

API: active pharmaceutical ingredient ; $AUC_{\infty}$: area under the plasma concentration-time curve from time 0 to infinite time; $AUC_{24h}$: area under the plasma concentration-time curve during the 24-hour dosing interval; CI: confidence interval; $C_{max}$: maximum observed plasma concentration; GMR: geometric mean ratio; NPE: non-particle-engineered; PE: particle-engineered; PK: pharmacokinetics

# Bioavailability Study in Dog (100 mg dose)

| Parameter | NPE API Lot 1 d10/50/90 9/29/101 µm (n=4) | PE API Lot 2 d10/50/90 21/51/104 µm (n=4) | PE API Lot 3 d10/50/90 2/6/14 µm (n=4) |
|---|---|---|---|
| $T_{max}$, h | 2.50 | 1.25 | 0.625 |
| $C_{max}$, ng/mL | 10100 | 10600 | 10200 |
| $AUC_{48h}$, ng.h/mL | 150000 | 145000 | 131000 |

- Although a lower mean $T_{max}$ was observed for the specially produced narrower particle size distribution, only small differences in $C_{max}$ (less than 5%) and AUC (less than 15%) were observed among the 3 API lots
- These results were consistent with GastroPlus findings

API: active pharmaceutical ingredient; $AUC_{48h}$: area under the plasma concentration-time curve during the 48-hour dosing interval; $C_{max}$: maximum observed plasma concentration; NPE: non-particle-engineered; PE: particle-engineered; PK: pharmacokinetics

# Conclusion

Differences in particle size distribution between NPE API and PE API lots would not cause any meaningful differences in the oral bioavailability of canagliflozin tablets and ultimately not affect the exposure of canagliflozin

API: active pharmaceutical ingredient; NPE: non-particle-engineered; PE: particle-engineered.

# Regulatory Feedback

## Query

Does the Agency agree that the **data package** to support drug product lots using NPE and PE API is **sufficient** and that results from **completed Phase 1 studies** using NPE API can be used to **support clinical pharmacology and biopharmaceutics labeling statements** and that a **relative bioavailability study** comparing drug product lots using NPE and PE API is **not required**?

## FDA Response

Although the approach used to compare NPE and PE API appears reasonable, the answer to this question is review issue.

If the conclusions drawn in the current submission can be confirmed, a relative bioavailability study is not needed. Please submit detailed information to the NDA, including the following:

1. The physicochemical property data, including the intrinsic dissolution profile comparison.
2. The GastroPlus model and simulation details, including description, assumption and validation for the model. Also include the scenarios, parameters and the interpretations for the simulation.
3. The data for each trial used in the cross-study comparison.

API: active pharmaceutical ingredient; NDA: new drug application; NPE: non-particle-engineered; PE: particle-engineered

Janssen received approval of NDA based on the successful review

# Acknowledgements


- Dr. Damayanthi Devineni – clinical pharmacology leader
- Dr. Christophe Tistaert – canagliflozin absorption modeling lead

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# Q&A