SDC Slovenia
Clinical Development

BCS3 compounds: In Vivo experience with non-Q1/Q2 formulations

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Background

Biopharmaceutics Classification System (BCS) [1]

- Class I: high solubility, high permeability
- Class II: low solubility, high permeability
- Class III: high solubility, low permeability
- Class IV: low solubility, low permeability

Background

In vivo bioequivalence studies may be waived for immediate release formulations with not narrow therapeutic index BCS1 and BCS3 compounds provided [2]:

- Dissolution: BCS1 - rapid or BCS3 - very rapid
- Adequate stability in GIT
- Excipients similarity:
  - BCS1: excipients that may affect absorption - qualitatively the same and quantitatively similar
  - BCS3: all excipients qualitatively the same and quantitatively very similar

Excipients

Impact on :

- permeability across intestinal epithelium [3]:
  - tight junctions
  - membrane fluidity
  - transporters
- intestinal transit[10]

Permeability: Caco-2 cells - more sensitive compared to native intestinal tissue and to In Vivo results [4,5].

Small quantities of certain excipients can influence bioavailability of some compounds [6].

Bioequivalence risk

Are bioequivalence studies with BCS3 compounds more risky ?

Source	Success of bioequivalence studies (%)		
	BCS1	BCS3	BCS2
Lamouche S et al., [7]	89	89	72
Cristofoletti R et al., [8]	84	90	60
Ramirez E et al., [9]	85	85	50

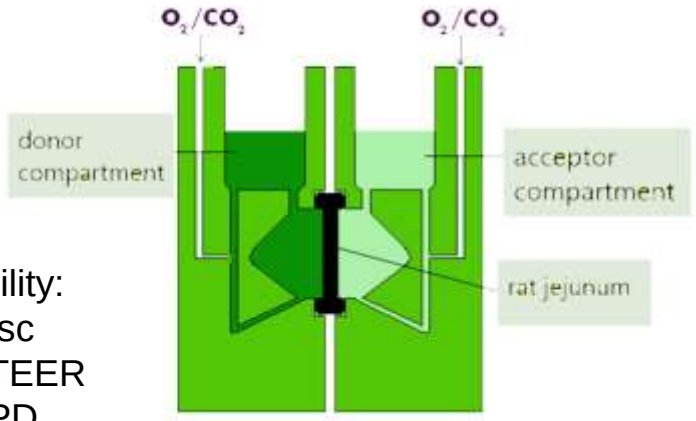
Sandoz experience with BCS3 studies (10+ years)

Bioequivalence studies with immediate release BCS3 formulations:

- 16 INNs
- 25 different formulations
- 83 studies
  - 34 with mono and 49 with combo product
  - 66 under fasting and 17 under fed condition
  - 70 (84 %) qualitatively **different** formulation as reference (non-functional coating excluded)
  - 82 (99 %) successful studies

Case 1: Presence of „critical“ excipient

- Immediate release formulation, BCS3 compound
  - Reference: Compound
  - Test: Compound in the form of Hydroxypropyl-β-cyclodextrin complex (HP- β-CD)



Viability:
- Isc
- TEER
- PD

Rat jejunum, Side-by-side diffusion chamber, pH=6.85, 37°C

	Compound	Compound - HP- β-CD complex
P_{APP} (x10^{-6} cm/s)	3.38 ± 0.22	3.51 ± 0.18
TEER (ohm×cm^2)	32.9 ± 5.4	34.5 ± 2.5
PD (mV)	-1.11 ± 0.13	-1.03 ± 0.09
Isc (µA/cm^2)	34.7 ± 2.7	31.2 ± 4.4

N=3, average ± SEM

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Case 1: Presence of „critical“ excipient

Comparative, Single-Dose, 2-way Crossover Bioavailability Study in 36 Healthy Adult Male Volunteers under Fasting Conditions

Comparison	Parameter	Ratio	Lower 90% CI	Upper 90% CI	
T vs R	C_{max}	94	88	100	✓
T vs R	AUC_t	102	98	106	✓
T vs R	AUC_i	102	99	106	✓

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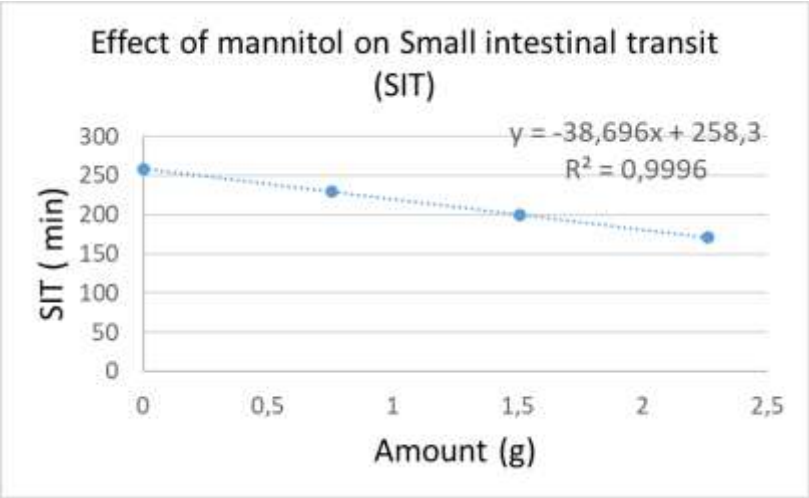
Case 2: Q2 difference in „critical“ excipient

- Granules for oral solution, BCS1/2 compound (salt of an acidic drug)
  - Reference: 1.70 g mannitol
  - Test: 1.82 g mannitol

→ 7% difference



→ 2% difference in SIT

Data taken from [10]

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Case 2: Q2 difference in „critical“ excipient

Comparative, Single-Dose, 2-way Crossover Bioavailability Study in 26 Healthy Adult Volunteers under Fed Conditions

Comparison	Parameter	Ratio	Lower 90% CI	Upper 90% CI	
T vs R	Cmax	105	97	113	✓
T vs R	AUCt	96	94	99	✓

Conclusions

- BCS1 and BCS3 compounds bring similar bioequivalence risk to IR formulations
- Q1 difference in excipients does not represent a major risk for bioequivalence for BCS3 containing IR formulations
- Impact of Q1 and Q2 difference in „critical“ excipients on drug absorption should be evaluated on a case by case basis

References

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Acknowledgment

Sandoz Product Development

- Clinical Development
- IVIVC

Thank you

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