Where top-down meets bottom-up: Combined population PK (PopPK) and PBPK approaches to evaluate the impact of food and gastric pH on the pharmacokinetics of GDC-0941

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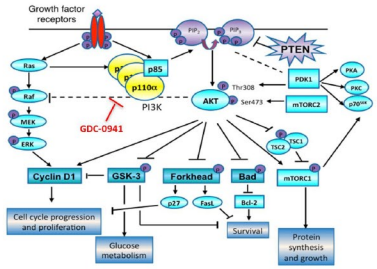
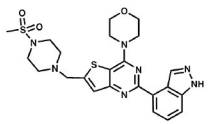
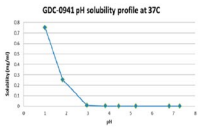
Background



- The phosphoinositide 3-kinase (PI3K) signaling pathway is deregulated in a wide variety of cancers. GDC-0941 is a potent and selective pan-inhibitor of class I PI3K. It demonstrates excellent *in vivo* activity in tumor xenograft models and is currently in clinical drug development.
- GDC-0941 is in multiple clinical trials for various cancers (e.g. BC, mBC, NSCLC).
- Based on its physicochemical properties – high permeability and poor solubility at physiologically relevant pH values (4 – 7.5), GDC-0941 classifies as BCS class II drug. GDC-0941 belongs to the group of compounds known for their highly variable absorption that is dictated by their solubility vs. pH profile characteristics.
- Because of the steep pH-dependent solubility profile in vitro, a Phase I, randomized, open-label study was conducted in healthy volunteers to investigate the effect of food and proton pump inhibitor (PPI) on GDC-0941 PK. PPI and food significantly impact the absorption process of GDC-0941.





Methods

OBJECTIVE

To develop the mechanistic PBPK model and popPK model to explain how pH and food impact GDC-0941 (Pictilisib) bioavailability in Healthy Volunteers

CLINICAL STUDY

- **Single-center, open label, two parts study (see poster PII-040)**

➢ Part 1 (Relative Bioavailability): 4x15 mg Capsule / 3x20 mg Prototype Tablet (n=18); Fasted state.

Sequence 1 : Prototype Tablet → PhI Capsule

Sequence 2 : PhI Capsule → Prototype Tablet

➢ Part 2 (Food and PPI Effect): 2x20 mg GDC-0941 Prototype Tablet (n=32)

Sequence 1 : Fasted → Fed → Fasted/PPI → Fed/PPI

Sequence 2 : Fed → Fasted → Fed/PPI → Fasted/PPI

METHODS

- **Both the top-down (PopPK) and bottom-up (PBPK) modeling approaches were used to quantitatively understand the factors that influence GDC-0941 PK (based on Part 2 data).**
- **PopPK analysis and covariate selection was conducted based on all data (134 subject with 1400 samples) using NONMEM v.7.2. Impact of food (fasted vs. fed), PPI (yes/no), formulation (capsule vs. tablet) on Ka, relative bioavailability and lag time were examined.**
  - Covariate effects were judged for their significance on basis of a likelihood ratio test at a p-value of 0.01 for forward inclusion and 0.001 for backward deletion.

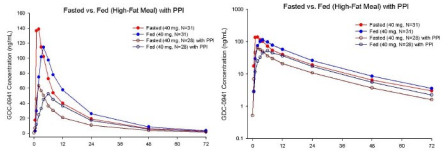
METHODS

- **PBPK analysis was conducted for group mean and representative subjects based on part 2 data using GastroPlus™ v.8.0. System parameters in the PBPK model (stomach transit time, precipitation time, and stomach pH) were adjusted to mimic the effect of food and PPI on GI physiology.**
  - As the input parameters, the physicochemical and biopharmaceutical properties were defined using in vitro measured values and in silico estimates from the ADMET Predictor™ v. 6.5 that are based on structure.
  - Intestinal absorption was described by the Advanced Compartmental Absorption and Transit (ACAT™) model in GastroPlus. The ACAT model accounted for the local solubility, dissolution, precipitation, and absorption of GDC-0941 in each region of the intestinal tract. Stomach transit time, precipitation time, and stomach pH were adjusted to mimic the effect of food and PPI on GI physiology.

Results

MEAN PLASMA CONCENTRATION-TIME PROFILE

- **40 mg GDC-0941 Tablet ± 20 mg Rabeprazole (fasted or fed)**

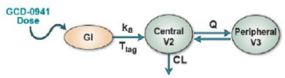


Treatment	C_{max} GMR (90% CI)	$AUC_{0-\infty}$ GMR (90% CI)
High fat meal	0.87 (0.70, 1.06)	1.28 (1.08, 1.51)
PPI fasting	0.31 (0.21, 0.46)	0.46 (0.35, 0.61)
PPI + high fat meal	0.43 (0.37, 0.50)	0.57 (0.50, 0.65)

POPPK AND COVARIATE ANALYSIS BASED ON 2 PARTS OF DATA

- **PK model:**

Two-compartment model with first-order absorption with lag time (Tlag) and first-order elimination from the central compartment.

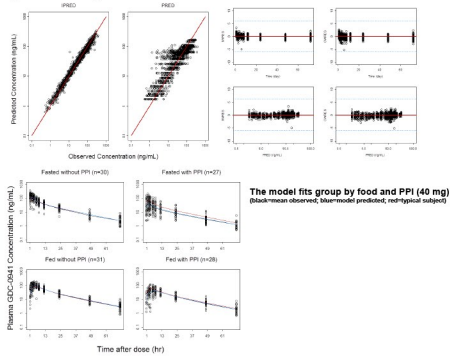


- **PK model parameters:**

Parameter		Unit	Typical Value	BSV
Absorption Rate Constant (ka)	Fasted	1/h	1.32	52.2%
	Fed		0.39	
Absorption Lag Time (Tlag)		h	0.56	71.3%
Clearance (CL/F)		L/h	25.3	49.8%
Distribution Clearance (Q/F)		L/h	22.9	9.95%
Central Volume (V2/F)		L	265.1	83.3%
Peripheral Volume (V3/F)		L	210.6	18.8%
Relative Bioavailability	PPI=0, fasted	%	100	
	PPI=1, fasted		65.6	
	PPI=0, fed		113.2	
	PPI=1, fed		78.8	
Residual Error (Proportional)			35.4%	

- ✓ Typical value of ka will decrease by ~70 % with food;
- ✓ Relative bioavailability will decrease by ~30% with PPI, regardless of food
- ✓ Relative bioavailability will increase by 10~20% with food, regardless of PPI
- ✓ Absorption lag time (Tlag) might not be affected by food and/or PPI.

- **Key model diagnostic results: :**



The model fits group by food and PPI (40 mg)
(black=mean observed; blue=model predicted; red=typical subject)

PBPK ANALYSIS RESULTS

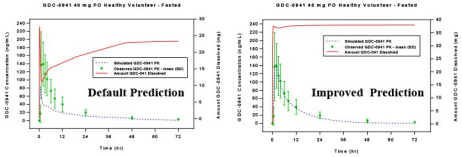
- **Key physicochemical and biopharmaceutical properties of GDC-0941 used in GastroPlus simulations**

Property	Value	Reference
logP	3.22	Measured
Diffusion coefficient	0.58 x 10^{-5} cm/s[2]	ADMET Predictor
pKa	Base: 4.24, 1.54	Measured
Aqueous solubility	0.001 mg/mL @ pH 6.78	Measured
Solubility Factor	697	ADMET Predictor
FaSSIF solubility	0.001 mg/mL	Measured
FeSSIF solubility	0.006 mg/mL	Measured
Bile salt solubilization ratio	27 700	GastroPlus calculated value[a]
Human effective permeability (P_{eff})	2.26 x 10^{-4} cm/s	Converted from Caco-2 Papp
Particle radius	16 μm	Measured
Precipitate radius	1 μm	GastroPlus default value
Drug particle density	1.2g/mL	GastroPlus default value
Mean precipitation time	900 s @ pH 1.3; 9 x10^{5} s @ pH 7.4	GastroPlus default value and fitted[b]
Blood:plasma concentration ratio (R_{bp})	1	Measured
Plasma protein binding (Fup)	5 % unbound	Measured
Adjusted plasma protein binding (Fup)	3.32 % unbound	GastroPlus default value[c]
Hepatic/total Cl	5 ml/min/kg	Estimated from HLM and human data

[a] GastroPlus default bile salt solubilization ratio is calculated from inputs of FaSSIF, FeSSIF and aqueous solubilities [GP manual].
[b] GastroPlus default value of 900 s was used for precipitation time in the intestine.
[c] Adjusted Fup was calculated from experimental Fup and logD @ pH = 7.4 using the default GastroPlus equation [GP manual].

- **Modeling Average Plasma Concentrations**

➢ **Fasted condition (without PPI)**



Absorption properties:

- ✓ High intestinal permeability and moderate solubility at fasted stomach (pH 1.3).

Default setting: Underpredicted Cmax, Tmax, and AUC

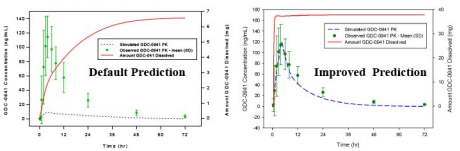
Reason for the underprediction:

- ✓ The default fasted stomach transit time (STT) of 0.25h was too short, given the slower dissolution of this moderately soluble compound even at pH 1.3. The default precipitation time (900s) overestimated precipitation potential of GDC-0941 triggered by pH gradient between the stomach and small intestine.

How to improve:

- ✓ Increase the STT (1h) to account for delayed gut absorption
- ✓ Long Tprecip (90000s) to account for the supersaturation tendency of GDC-0941

➢ **Fed condition (without PPI)**



Absorption properties: Very poor solubility at pH 4.9 as a weak base

- ✓ Very poor solubility at pH 4.9 as a weak base
- ✓ Very slow precipitation due to the presence of food and bile salts.

Default setting: Significantly underestimated overall exposure

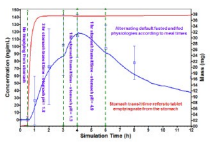
Reason for the underprediction:

- ✓ The very poor solubility at default stomach fed pH (4.9) led to minuscule amount dissolved.
- ✓ Default fed STT (1h) was too short to account for a long dissolution time (tablet could not leave the stomach until it disintegrated and at least partially dissolved). The default Tprecip (900s) overestimated precipitation potential of GDC-0941 under fed condition.

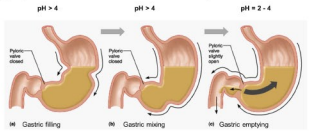
How to improve:

- ✓ Increase the STT and adjust the stomach pH to reflect meal times and stomach emptying anatomy.

Time (h)	Stomach TT (h)	Stomach pH
0	100	4.9
0.5	3	1.8
3	1	1.3
4	1	4.9
6	0.25	1.3

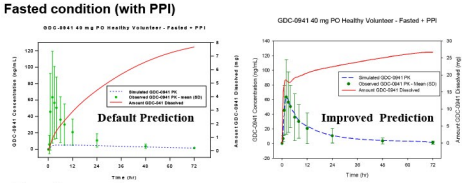


- ✓ Stomach emptying does not occur until its contents reach pH around 2~4



- ✓ Long Tprecip (90000s): to account for the supersaturation tendency of GD-C0941 in the stomach, and the lack of precipitation under fed condition.

➢ **Fasted condition (with PPI)**



Absorption properties:

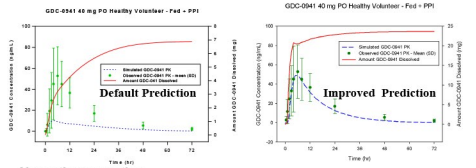
- ✓ Increased pH, decreased solubility and increased STT due to the presence of PPI (the impact of PPI on STT and pH is highly variable between subjects)

Default setting with PPI effect on pH: Significantly underestimated overall exposure

Reason for the underprediction: Mainly due to high stomach pH (4.5, the high boundary for fasted with PPI), which lead to decreased solubility; The short STT (0.25h) and Tprecip (900s).

How to improve: Decrease pH to 2.2 (within the pH range for fasted with PPI: 1.8 ~4.5); Increase STT (1h) to delay gut absorption; Increase Tprecip to 7000s

➢ **Fed condition (with PPI)**



Absorption properties:

- ✓ Increased pH, decreased solubility and increased STT due to the presence of PPI and food;
- ✓ Impact of PPI on pH overweight the pH change due to food effect

Default setting with PPI effect on pH:

- ✓ Significantly underestimated overall exposure; lag time not accounted for.

Reason for underprediction: Mainly due to high stomach pH (7.0, the high boundary for fasted with PPI), which lead to decreased solubility; The short STT (1h) and Tprecip (900s)

How to improve: Decrease pH to 2.5 (within the pH range for fed with PPI: 2.0 ~ 7); Increase STT (1h) to delay gut absorption; Increase Tprecip to 90000s

Time (h)	Stomach TT (h)	Stomach pH
0	100	4.9
1	3	2.5
4	3	4.9

Conclusions

- As a weak base with pKa values of 4.2 and 1.5, GDC-0941 belongs to the group of compounds with solubility-limited absorption and supersaturation tendency.
- PopPK analysis suggested a decrease of absorption rate constant and a increase of relative bioavailability with food, regardless of PPI; and also suggested a decreased relative bioavailability by PPI, regardless of food.
- PBPK modeling was conducted for group mean and individuals (not shown) using GastroPlus™ v. 8.0 to understand the impact of food and PPI on the PK of GDC-0941.
- The PK of fasted group could be well-predicted using default fasted physiology, with longer stomach transit time and precipitation time, indicating that GDC-0941 forms supersaturated solution in the stomach. Higher than expected absorption in fed state was explained by increased dissolution due to the long residence time in stomach - until food emptied and stomach pH dropped to around 2~4. The PK of fed and fasted groups with PPI was well-predicted by considering the smaller than expected increase in gastric pH and delayed gastric emptying.
- The PBPK approach provided mechanistic explanation for different absorption rate constant and bioavailability under different physiological conditions, which were confirmed by the PopPK covariate screening. PBPK modeling helped to quantify the determinants of GDC-0941 absorption and was applied to explore hypochlorhydria mitigation strategies.
- Model translation from healthy volunteer to oncology setting is currently underway.

- **Reference:**

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