Introduction
Bariatric surgery, involving partial restriction of the gastrointestinal (GI) tract, has proven to be clinically and cost effective for treating morbid obesity [1]. Oral drug bioavailability (BA) is dependent on physiological parameters, such as gastric emptying, pH, small intestinal transit (SITrans) and regional abundances of drug metabolising enzymes and efflux transporters [2]. These parameters are altered to differing extents following surgery. Roux-en-Y gastric bypass (RYGBP) and bilipancreatic diversion with duodenal switch (BPDDS) lead to a reduction in gastric volume, bypass of the proximal small intestine and delayed bile inlet compression, whereas sleeve gastroectomy (SG) [3], results in a reduced gastric volume. As a consequence of these events, altered oral drug exposure has been reported following bariatric surgery [4].

The Advanced Dissolution Absorption Metabolism (ADAM) model, incorporated into the population-based PKPD simulator Simcyp, is an in silico mechanistic platform for integrating in vitro data and predicting oral BA. The model considers all available information related to regional intestinal abundances of CYP3A and relative distribution of g-glycoprotein (P-gp) efflux transporters in addition to the segregated blood flows to each region of intestine (Figure 1) [2]. ADAM might be used to assess expected BA in various GI surgeries.

Objectives
To examine the impact of bariatric surgery on oral BA of drugs in morbidly obese patients through incorporation of post surgery anatomical, physiological and biological changes into a mechanistic modelling framework, and to assess trends in AUC, F, (fraction of dose absorbed) and F2 (fraction escaping gut wall metabolism).

Methods
An extensive literature search was carried out to obtain anatomical, physiological and biological parameters corresponding to bariatric surgery. The ADAM model of the Simcyp Stimulator (v10) was adapted to mimic the changed identifications in the GI tract. Due to conflicting literature data regarding SITrans following surgery, two scenarios were evaluated, one corresponding to a reduction in SITrans and related to the extent of bypass, and the other reflecting an increased transit time recorded following Roux-en-Y with total gastrocytomy [5]. Simulations were carried out for 3 therapeutic dose levels (low, medium and high) of each drug: immediate release (IR), osmoprenal [enteric coated (EC)], diclofenac [EC], cyclosporine [IR] and ciprofloxacin [IR]; in 100 virtual morbidly obese, post surgical (RYGBP, BPDDS and SG) patients.

Results
Population Characteristics
The post RYGBP population template displayed a gastric emptying of 7 (+/-3) minutes, restricting fluid intake to 30 mL as compared to 250 mL in morbidly obese. Gastric Jjej1 pH was set to 6.4. The small intestine bypass corresponded to ADAM model segment Duo and Jjej1 (88 cm); whereas the bile inlet was diverted to Jjej2 segment (113 cm; Figure 1). Small intestinal transit (SITrans) was set to 2.2 and 5.0 hours [2,3,6,7]. In the post BPDDS population fluid intake was restricted to 150 mL. Segments Jjej1 and 2 were bypassed (132 cm); whereas the bile inlet was diverted to Jjej3 (322 cm) (Figure 1). Small intestinal transit (SITrans) was set to 2.2 and 3.3 hours [2,3].

Further, regional abundances of CYP3A were adjusted in accordance to the small intestinal bypass, through recalculating total and regional gastrointestinal abundances [2].

Simulating oral drug exposure
Following RYGBP (ST=5h) simvastatin (low solubility, eliminated via CYP3A1) [17,18] displayed an increase in AUC at a low therapeutic dose, with a mean post/pre surgery ratio of 1:1.8, becoming less apparent at 12h post dose [16]. The latter was consistent with a reported reduction in AUC following jejuno-ideal bypass [21]. The results provide insight into factors influencing the BA of each drug following surgery (solubility, reduced absorptive area, time for absorption and altered gut wall metabolism). The impact of each of these factors is specific to each type of surgery. Hence, the consequential change in BA is a complex interplay between drug characteristics and modifications to the GI tract in each surgery. ADAM may be an ideal tool to estimate these in the absence of clinical data.

Discussion and Conclusions
Simvastatin displayed the most significant increase in BA, due to reduced exposure to intestinal CYP3A; whereas cyclosporine showed the most extensive reduction in BA following surgery, as a possible consequence of delayed bile inlet [20]. The latter was consistent with a reported reduction in AUC following jejuno-ideal bypass [21]. The results provide insight into factors influencing the BA of each drug following surgery (solubility, reduced absorptive area, time for absorption and altered gut wall metabolism). The impact of each of these factors is specific to each type of surgery. Hence, the consequential change in BA is a complex interplay between drug characteristics and modifications to the GI tract in each surgery. ADAM may be an ideal tool to estimate these in the absence of clinical data.

Acknowledgements
Authors wish to thank Prof. Darren Ashcroft, Mr Basel Ammoni and Dr Nicola Ward.

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