## Title: Using partial AUC to characterize the impact of shape of pharmacokinetic profiles on bioequivalence evaluation **PRESENTER**:

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## **BACKGROUND:**

AUC and C<sub>max</sub> are routinely employed to assess bioequivalence (BE) between the two products. However, situations may merit additional or alternative metrics to characterize the impact of the shape of pharmacokinetic profiles on BE.

The objective of this study was to summarize the use and recommendations for partial area under the curve (pAUC) and other metrics (e.g.,  $C_{max}$ , AUC<sub>0-t</sub> and AUC<sub>0-inf</sub>) to compare pharmacokinetics (PK) profiles based on review of literature.

## **METHODS**

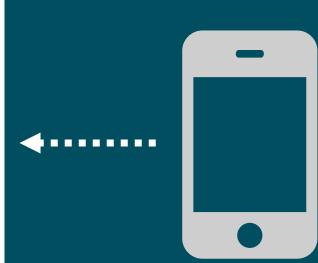
1. An extensive literature search was conducted using OVID-Medline and PubMed up to August 2020.

2. Key mesh terms included PK terms: partial AUC, therapeutic equivalency and bioequivalence. Also included were names of several drugs with the desire of pAUC evaluation based on our prior knowledge: budesonide, mesalamine, methylphenidate, amphetamine, zolpidem, scopolamine, sumatriptan, hydrocodone, morphine, oxycodone, and naloxone. Also included were eight indications for which early onset, sustainable or targeting effect is needed: Crohn's, ulcerative colitis, Attention Deficit Hyperactivity Disorder (ADHD), insomnia, nausea, migraine, pain and opioid overdose. 3. Combinations of PK terms, drug names and disease indications were used to search for key articles.

# pAUC generally involved the consideration of the onset of drug action and sustained effect. pAUC recommendations can depend on T<sub>max</sub> or desired effective time considerations.

When to recommend	How to recommend (e.g., based on T <sub>max</sub> , etc.)	Drug Product (given orally unless otherwise indicated)	Indications	pAUC recommendations	References	pAUC recommendations in
	<ol> <li>based on Tmax</li> <li>release characteristics</li> <li>abuse-deterrent formulation</li> </ol>	Oxycodone DETERx <sup>®</sup> 40 mg	Moderate to severe pain	AUC0-1.75 hour	Gudin et al. Pain Med. 2015. doi:10.1111/pme.12834.	AUC up to time to maximum concentration (Tmax) (e.g., AUC and AUC0-4 hour).
	<ol> <li>based on Tmax</li> <li>PK/PD relationship</li> </ol>		Reversal of opioid overdose	AUCO-1min, AUCO-2min, AUCO-4min, AUCO-10min, AUCO-20min and AUCO-30min		<ul> <li>AUC of early time points as sugdata to assess the onset of nalox effect.</li> <li>Compare exposure to naloxone T and the R product within the f minutes, 10 minutes, and 10-30 after administration.</li> </ul>
	<ol> <li>based on Tmax</li> <li>release characteristics</li> </ol>	6 mg subcutaneous sumatriptan, 25 mg sumatriptan oral tablet, 25 mg sumatriptan suppository and 20 mg sumatriptan intranasal spray.	Migraine	AUCO-tmax Median Tmax: S.c., 6mg = 0.17 hour Oral, 25mg = 1.50 hour Suppository, 25mg = 1.00 hour Intranasal, 20mg =1.50 hour	Sci. 1998. doi: 10.1016/s0928- 0987(97)00073-0.	pAUC was not mentioned in PSG
	<ol> <li>based on Tmax</li> <li>release characteristics</li> </ol>	Amphetamine XR tab (AMP XR- ODT (fasted or fed) or MAS ER (fasted))	ADHD	AU0-5 hour, AUC5-last		All amphetamine products: AUC AUC5-t to evaluate drug bioavail the rapid onset and sustained maintenance of the clinical response throughout the 24-hour dosing in
	<ol> <li>based on Tmax</li> <li>release characteristics</li> </ol>	Amphetamine ER Oral Liquid Suspension (AMP XR-OS) (fasted/fed) Extended-release mixed amphetamine salts (MAS ER)† ONLY under fed conditions.	ADHD	AU0-5 hour, AUC5-last	Sikes et al. Clin Ther. 2017. doi: 10.1016/j.clinthera.2017.10.01 8.	
	<ol> <li>based on Tmax</li> <li>release characteristics</li> <li>food-impact</li> </ol>	Methylphenidate ER – ODT: two 30-mg tablets given under fed or fasted conditions.	ADHD	AUC0-3 hour, AUC3-7 hour and AUC7-12 hour	Weisler et al. Clin Pharmacol Drug Dev. 2018. doi: 10.1002/cpdd.361.	• AUCT1-T2 for sustaining the re the middle of the once-daily dos
	1) based on Tmax 2) release characteristics	Methylphenidate modified release product with a bi-model release profile	ADHD	AUC0-4hour, AUC0-6hour		
	<ol> <li>based on Tmax</li> <li>release-characteristics</li> <li>food-impact</li> </ol>	MPH IR products MPH MMR (Multiphasic Modified Release) formulations (Ritalin LA®)	ADHD	AUCO-3 hour (fast), AUCO- 4hour (fed), AUC3-T (fast), and AUC4-T (fed)		
	PK/PD relationship and desired effective time	Zolpidem IR and Zolpidem tartrate ER tablets	Insomnia	AUC0-1.5 hour, and AUC1.5-t		AUCO-1.5 hour and AUC1.5-t to e the sleep onset and sleep mainte phases, respectively.





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### RESULTS

1. There were 92 article hits, spanning from 1998 to 2019. The majority of article hits did not calculate a pAUC or provided pAUC calculation as recommended in FDA's productspecific guidances (PSGs) (e.g., AUC<sub>0-4hr</sub> for methylphenidate immediate release (IR) product). Some articles provided pAUC calculation but were deemed not feasible (e.g., AUC<sub>0-1min</sub> for naloxone nasal spray). 2. Out of these 92 articles, 9 representative articles provided recommendations about the use of pAUC to compare PK profiles for BE assessment

3. As shown in Table 1, situations to recommend pAUC include: rapid onset and rapid onset plus sustained effect, but not targeting effect due to lack of articles. pAUC was in general recommended based on T<sub>max</sub> or desirable effective time period.

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