Bridging from conventional marketed extended release formulations to new tamper resistant alternatives.

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intac™ by Grünenthal

Introduction

Conventional extended-release (ER) formulations containing opioid substances are often subject to abuse and misuse. Many of these tablets can be easily chewed or crushed resulting in compromising the ER properties. Additionally, once crushed the ER tablets can be snorted or injected.

Oral tablet formulations known as tamper resistant formulation (TRF) have been developed to counteract this problem and thereby also enhance patients' safety. Grünenthal (GRT) has developed a TRF technology (INTAC™) with increased tablet hardness using a high molecular weight polymer.

The INTAC™ tablet exhibits:

- a high breaking force
- and forms a viscous gel when exposed to an aqueous medium

These unique physical characteristics provide the tablets with tamper resistant properties, thereby significantly reducing the potential for unintended misuse or intended abuse[1]. The INTAC™ technology is featured in FDA approved products. The INTAC™ tablet formulations of an analgesic described here have been developed in 6 tablet strengths which have similar release profiles to the marketed extended release formulations.

A switch from a conventional ER formulation to safer drug product alternatives requires bridging studies. Currently however, no clear regulatory guidance is available for conducting such a switch. Importantly the number of trials depends on the number of dose strengths and proportionality of composition.

One example for a life cycle management program aligned with a national EU health authority is presented here.

Methodology

Study Program

A set of eight (out of 18 possible) single (SD) and multiple dose (MD) BE trials was conducted investigating 6 different dose strengths of an analgesic with a factor of 10 from the lowest to the highest dose (see table below). The qualitative composition of the tablets is identical whereas they differ quantitatively in terms of the active substance/ingredients ratios.

Bioequivalence trials

Dose strength (DS)	SD fasted	SD fed	MD
DS1 (lowest)	X		
DS2	X	X	
DS3	X		X
DS4			
DS5			
DS6 (highest)	X	X	X

Table 1: Display of BE bridging program

Substantially fewer trials would be required for a simpler case with less dose strengths and/or composition proportionality.

Studies

- open, randomized, two-treatment, two-period, two-sequence cross-over design
- wash-out period between the administrations: 5–14 days
- single and multiple dose administrations
- fasted and fed conditions

The studies were performed according to the current European CPMP guideline CPMP/EWP/280/96 (1999)[2], were regularly monitored and audited according to GLP and GCP. All bioanalytical procedures were performed following GLP.

Subjects

- up to 44 healthy male Caucasian subjects (per study) aged 18–55 years with a BMI range of 18.5–30 kg/m²

Pharmacokinetic (PK)/Statistical Evaluation

- non-compartmental analysis for TRF (Test) and conventional ER (Reference) formulations
- parametric (ANOVA) point estimates and 90% confidence intervals calculated for the ratios Test/Reference of C_{max}, AUC_{0-t} (single dose) and $C_{max,ss}$, $C_{min,ss}$ and $AUC_{tau,ss}$ (multiple dose).
- Test was considered bioequivalent to Reference if the 90% confidence intervals for key PK parameters fell within acceptance range of 80%–125%.

Safety/Tolerability Evaluation

- physical examination, vital signs, electrocardiogram, adverse events, hematology, clinical chemistry, urinalysis.

Results

Pharmacokinetics/Statistics

Demographics:

- 339 healthy Caucasian male subjects enrolled into the bridging program
- 320 completed as per protocol
- ages 18 to 55 years
- overall body weights ranged from 56 to 107 kg

Selected results from the different BE trials are presented to show the overall similarity of the new TRF and the standard marketed ER formulations. Sample geometric mean serum concentration-time curves after single dose and multiple dose administration are shown in Figure 1.

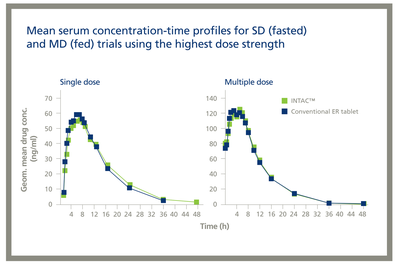


Figure 1: Geometric mean concentrations of analgesic drug [ng/mL] vs. time [h] following SD and MD oral administration of Test and Reference (n=44).

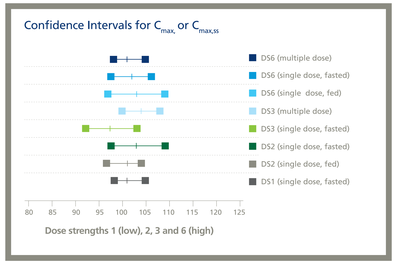
- T_{max} after single dosing 5–6 hours
- T_{max} after multiple dosing 3–5 hours

A graphical overview of calculated 90% confidence intervals from all conducted BE trials is shown in Figure 2.

As can be seen from the graphs all confidence intervals fell well within the 80–125% acceptance range for bioequivalence.

The minimum and maximum values of the statistical analyses for the primary pharmacokinetic parameters C_{max} and AUC_{0-t} of 6 single dose fasted and fed trials are tabulated in Table 2.

The minimum and maximum values of the statistical analyses for the primary pharmacokinetic parameters, $C_{min,ss}$, $C_{max,ss}$, and $AUC_{tau,ss}$ of 2 multiple dose trials are tabulated in Table 3. The similarity of both formulations is demonstrated by fulfilment of BE criteria and by the majority of point estimates being close to 1.00.



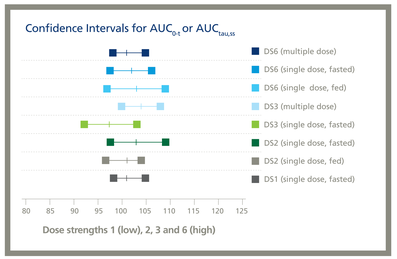


Figure 2: 90% Confidence Intervals for C_{max} or $C_{max,ss}$ and AUC_{0-t} or $AUC_{tau,ss}$ of analgesic drug in 8 bridging trials with 6 different dose strengths.

PK parameter	ANOVA CVs [%]*	Point estimates*	90% confidence intervals [%]*
Single dose trials			
C_{max}	10.0–17.5	0.97–1.14	91–119
AUC_{0-t}	8.3–16.5	0.79–1.03	92–109

Table 2: Intra-individual variation, point estimates and their 90% CI for selected SD PK parameters of analgesic drug

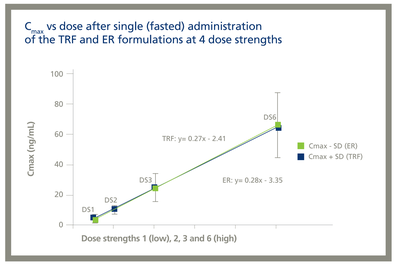
PK parameter	ANOVA CVs [%]*	Point estimates*	90% confidence intervals [%]*
Multiple dose trials			
$C_{min,ss}$ $C_{max,ss}$	11.2, 13.2 10.3, 12.4	1.05, 1.06 0.98, 1.00	100–111 94–105
$AUC_{tau,ss}$	8.8, 10.1	1.01, 1.04	98–108

Table 3: Intra-individual variation, point estimates and their 90% CI for selected MD PK parameters of analgesic drug

Cross trial evaluation:

- good dose linearity of exposure across the 10-fold dose range
- almost superimposable linear regression lines for the two formulations.

Based on the low intercepts, approximate dose proportionality for both C_{max} and AUC_{0-t} can be assumed.



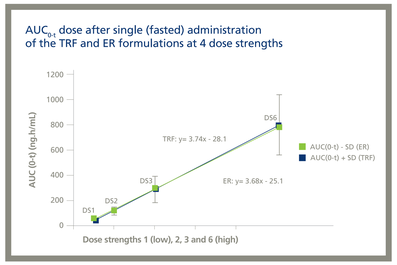


Figure 3: Cross trial presentation of mean C_{max} and AUC_{0-t} after 4 different dose strengths of test and reference formulation

Safety / Tolerability

- no reports of any difficulties in swallowing during the numerous administrations of INTAC™ during this trial series
- observed adverse event profile of INTAC™ in line with current experience with the marketed reference drug

Conclusion

Although INTAC™ tablets are extremely hard and difficult to tamper with, their in vivo performance is nonetheless comparable to the standard/marketed ER formulation:

- BE demonstrated for the new TRF formulation to the reference marketed ER product over a 10-fold range of dose strengths
- Similar times to reach maximum concentrations and prolonged release characteristics observed for both formulations
- AE profile of new INTAC™ tablets in line with marketed reference

Implementation of an aligned BE study program provided submission ready clinical data for the new INTAC™ formulation in less than one year.

- INTAC™ technology featured in FDA approved products
- Physicians can easily switch to reformulated TRF products

References

1 Vosburg SK, Jones JD, Manubay JM, et al.: Assessment of the ease with which prescription opioid abusers prepare a TRF versus a non-TRF for abuse. Presented at: the 73rd Annual Scientific Meeting of The College on Problems of Drug Dependence (CPDD); June 18-23, 2011; Hollywood, Florida:189. Abstract 753.

2 CPMP/EWP/280/96 (1999) Note for Guidance on Modified Release Oral and Transdermal Dosage Forms

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