Title

Optimising paediatric medicines development through early selection of the best accepted formulation with a scientifically sound composite endpoint method

Introduction

Justification of the formulation selection is a challenging element in paediatric development negotiations with authorities as no scientifically sound, broadly recognised acceptability assessment methods exist.

Method and Materials

The objective of this composite endpoint methodology was to enable front-loading of oral formulation selection with a standardised, statistically sound acceptability assessment method before entering the paediatric efficacy and safety studies.

In statistically powered paediatric patient studies with placebo-containing oral formulations, performed with standardised investigator-observed assessment methods and defined evaluation criteria for swallowability and palatability in children, statistically significant differences between the acceptability of several oral formulations were detected (Klingmann et al. [1-6]). To further strengthen the capability of discrimination, a new acceptability method was established combining a swallowability score and a palatability assessment. Data from 2 studies [5,6] investigating mini-tablets, oblong tablets, orodispersible films and syrup in patients from 6 months to below 6 years were used to investigate the composite endpoint's validity, expediency and applicability. The statistical procedure for validation of the composite endpoint is published [7] and will be explained in the poster/short presentation. A clinical trial to validate the composite endpoint over all paediatric age groups has recently been completed. The results will also be presented.

Results

A high association between acceptability categories and the results from factor analysis was recognized. Comparison of the acceptability categories with regard to the main component by analysis of variance yielded a p-value < 0.0001. All formulations showed highly consistent results demonstrating significantly better acceptance of mini-tablets and oblong tablets in comparison to syrup.

Conclusion

The suggested acceptability method combining swallowability and palatability in form of a composite endpoint can be regarded as a highly sensitive and reliable approach to early identification of most suitable oral formulations for different paediatric age groups. These comparative studies can be quickly performed in statistically defined patient cohorts before entering indication-specific efficacy or safety studies. Currently the composite endpoint method is undergoing the EMA Qualification Advice process suggesting the composite endpoint as standard acceptability assessment method for acceptability of oral paediatric formulations.

References

1. Spomer N, Klingmann V et al., Acceptance of uncoated mini-tablets in young children: results from a prospective exploratory cross-over study, Arch Dis Child, 2012; 97:283-286

2. Klingmann V et al., Favourable acceptance of mini-tablets compared to syrup: a randomised controlled trial in small children, J Pediatr, 2013; 163:1728-1732

3. Klingmann V et al., Acceptability of uncoated mini-tablets in neonates - a randomized controlled trial, J Pediatr, 2015;167:893-896

4. Klingmann V et al., Acceptability of multiple uncoated mini-tablets in infants and toddlers: A randomized controlled trial, J Pediatr, 2018; 201:202-207

5. Klingmann, V et al., Acceptability of an orodispersible film compared to syrup in neonates and infants: A randomized controlled trial. Eur J Pharm Biopharm, 2020; 151:239-245

6. Münch J et al., Acceptability of Small-Sized Oblong tablets in Comparison to Syrup and Mini-tablets in Infants and Toddlers: A Randomized Controlled Trial. Eur J Pharm Biopharm, 2021; 166:126-134

7. Wargenau M et al., A Composite Endpoint for Acceptability Evaluation of Oral Drug Formulations in the Pediatric Population. Ther Innov Regul Sci., 2022; 56:903–909.

Authors

Viviane Klingmann, Düsseldorf

Sybille Reidemeister, Basel

Ingrid Klingmann, Wezembeek-Oppem

Manfred Wargenau, Düsseldorf