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Acceptability, Swallowability, and Palatability of Three Oral Placebo Formulations in Young Children

A Randomized, Single Dose, Two Parallel Groups, Monocentric Cross-over Study to Investigate the Acceptability, Swallowability, and Palatability of Three Oral Placebo Formulations in Young Children

Dissertation

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Teile dieser Arbeit wurden veröffentlicht:

"*Acceptability of small-sized oblong tablets in comparison to syrup and mini-tablets in infants and toddlers: A randomized controlled trial* [1]*"*

Zusammenfassung

Die Rate an *off-label* oder *off-licensed* verschriebenen Medikamenten im Kindesalter ist noch immer sehr hoch [2]. Die Abwesenheit adäquater oraler Darreichungsformen für Kinder stellt ein weiteres Problem dar [3].

Trotz Bemühungen der *Weltgesundheitsorganisation* (WHO) und der *European Medicine Agency* (EMA), gibt es nach wie vor wenige Studien zu alternativen Darreichungsformen im Kindesalter. In mehreren Studien wurde bereits die Gabe von Minitabletten unterschiedlicher Größe untersucht. Auch die Verabreichung multipler Minitabletten war im Rahmen von Studien möglich. Minitabletten stellen somit eine kindgerechte und sichere alternative orale Darreichungsform dar. Zur Gabe von kindgerechten Oblongtabletten lagen bislang keine Studienergebnisse vor. Die länglichen Tabletten (2,5 mm x 6 mm) könnten eine weitere Alternative zum häufig verabreichten Sirup darstellen. Durch diese neue Darreichungsform kann in einer Formulierung circa fünfmal so viel Wirkstoff wie durch eine Minitablette von 2 mm Durchmesser verabreicht werden. Die Akzeptanz, Schluckbarkeit und Schmackhaftigkeit der Oblongtablette wurden in einer offenen, randomisierten, einfach dosierten, altersstratifizierten zwei-fach-Cross-over-Design Studie mit 5 Altersgruppen (1-2 Jahre, 2-3 Jahre, 3-4 Jahre, 4-5 Jahre, 5-6 Jahre) mit dem bisherigen Goldstandard Sirup oder 3 Minitabletten mit 2 mm Durchmesser verglichen. Es wurden 280 Kinder in die Studie eingeschlossen. Es konnte gezeigt werden, dass die Akzeptanz der Oblongtablette der des Sirups über alle Altersgruppen (1 bis < 6 Jahre) nicht unterlegen war (84,4% vs. 80,1%, Differenz 4,3% Punkte mit 95% CI von -3,0%,11,6%, primärer Endpunkt). Hinsichtlich der Schluckbarkeit konnte nicht nur eine Nicht-Unterlegenheit, sondern auch eine Überlegenheit der Oblongtablette gegenüber Sirup nachgewiesen werden (74,5% vs. 53,2%, Differenz 21,3% Punkte, 95% CI von 11,3%, 31,2%). Beide unabhängigen Ärzte, welche die Reaktionen nach der Einnahme der Darreichungsformen beurteilten, befanden die Einnahme der Oblongtablette bei etwa 10% der Kinder als unangenehm, während bei einem weitaus höheren Anteil von etwa 40% der Kinder unangenehme Reaktionen nach der Einnahme von Sirup festgestellt wurden. Im Vergleich der Oblongtablette zur simultanen Einnahme dreier Minitabletten wurden bezüglich Akzeptanz, Schluckbarkeit und Schmackhaftigkeit keine signifikanten Unterschiede festgestellt.

Demzufolge sind Oblongtabletten eine praktikable und gut akzeptierte Alternative zum Goldstandard Sirup.

Abstract

The proportion of off-label or off-licensed medicines prescribed in childhood is still very high [2]. The lack of adequate oral dosage forms for children is a further problem [3]. Despite the efforts of the *World Health Organization* (WHO) and the *European Medicine Agency* (EMA), there are still few studies on alternative childhood dosage forms.

Several studies have already investigated the administration of mini-tablets of different sizes. The administration of multiple mini-tablets has also been investigated. Mini-tablets thus represent a child-friendly and safe alternative oral dosage form.

To date, no study results have been available on the administration of child-friendly oblong tablets. These longer tablets (2.5 mm x 6 mm) can be a further alternative to the frequently administered syrup. This new dosage form would allow approximately five times as much active ingredient to be administered as through a mini-tablet of 2 mm diameter. The acceptability, swallowability and palatability of the oblong tablet were compared to the previous gold standard syrup or 3 mini-tablets of 2 mm diameter in an open, randomized, single dose, age-stratified two-way cross-over design study with 5 age groups (1-2 years, 2-3 years, 3-4 years, 4-5 years, 5-6 years). 280 children were enrolled in the study. It was shown that the acceptability of the oblong tablet was not inferior to that of the syrup over all age groups (1 to <6 years) (84.4% vs. 80.1%, difference 4.3% points with 95% CI of -3.0%,11.6%; primary endpoint). Regarding swallowability, not only non-inferiority but also superiority of the oblong tablet over syrup was demonstrated (74.5% vs. 53.2%, difference 21.3% points, 95% CI of 11.3%, 31.2%). Both independent physicians, who assessed the reactions after taking the dosage forms, considered the intake of the oblong tablet as unpleasant in about 10% of the children, while in a much higher proportion of about 40% of the children unpleasant reactions were observed after taking syrup. No significant differences were found when comparing the oblong tablet to the simultaneous intake of three mini-tablets concerning acceptability, swallowability and palatability.

It can therefore be concluded, that oblong tablets are a feasible and well accepted alternative to the gold standard syrup.

List of abbreviations

ADME	Adsorption, distribution, metabolism, excretion
ADR	Adverse drug reaction
API	Active pharmaceutical ingredient
BPCA	Best Pharmaceuticals for Children Act
CI	Confidence interval
EC	European Comission
EMA	European Medicine Agency
e.g.	Exempli gratia
Etc.	Et cetera
EU	European Union
FDA	Food and Drug Administration
Fig.	Figure
GFR	Glomerular filtration rate
ICH	International Conference for Harmonization
i.e.	Id est
NIH	National Institute of Health
ODF	Orodispersible film
OL	Off-label
PD	Pharmacodynamics
PDCO	Paediatric Comimittee
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PREA	Pediatric Research Equity Act
PUMA	Paediatric Use Marketing Authorization
RCT	Randomized controlled trial
UL	Unlicensed
VAS	Visual Analouge Scale
vs.	Versus
WHO	World Health Organization

Table of Contents

1 Introduction

1.1 Background

1.1.1 Difficulties in development of medicines for the pediatric population

It is well known that children differ significantly from adults in terms of pharmacokinetics (PK) and pharmacodynamics (PD) [4]. However, there are also differences in the metabolism of drugs within the pediatric population. This heterogeneity is due to the fact that physiological functions develop considerably during childhood and adolescence. The pediatric population can therefore be divided into subgroups according to age [4, 5]. But still, since growth and development are not linear but vary from patient to patient, body weight or body surface are commonly used to determine the appropriate dosage of a drug [5].

As there are few trials in pediatric populations, data used in dosing of medication in children is often extrapolated from research results in the adult population [6]. The resulting absence of marketing authorization for medication in pediatrics causes many medicines to be given off-label (OL) or unlicensed (UL), which means that they are not approved in terms of age, weight, indications or routes of administration [7, 8]. Corny et al. published a review in 2015, which showed that 33.2% to 46.5% of pediatric inpatients and 3.3% to 13.5% of outpatients received off-label drugs [9]. 11.4% of drugs in pediatrics were prescribed unlicensed in inpatients and 1.3% to 6.2% in outpatients [9].

Relying on data from adult practice to prescribe drugs for children could have serious consequences for the patients including a higher risk of adverse drug reactions (ADR) [8, 10-12] which is defined by the WHO (World Health Organization) as "*a reaction to a drug (..) that is noxious, is unintended and occurs at doses normally used in man* [13]."

Furthermore, children often receive modified drugs like crushed tablets in liquid or segmented tablets due to a lack of age-appropriate galenic formulations [14]. Such manipulations of medicaments may lead to changes in stability, bioavailability, pharmacokinetics, pharmacodynamics, dosing accuracy, tolerability and reproducibility and are therefore no proper form of application [14-17]. In recent years, much has been done to raise awareness of the need for studies in pediatrics. But although the number of trials has increased, many medications are still prescribed off-label or unlicensed [11].

One reason for this may be the absence of adequate dosage forms [11].

1.1.2 Reasons for the deficiency of pediatric studies

Children made up 30% of the world population in 2020 [18]. Because this is a small percentage compared to the adult population, children are economically unattractive for pharmaceutical companies [19]. In addition, studies in children are more expensive than those in adults, because several studies in different age groups are required for marketing authorization [20]. Since most diseases occur significantly less frequently in children than in adults, the participants of these trials have to be recruited at many different sites over a prolonged period of time, which requires money and manpower. As sales are not particularly high in the pediatric population due to low demand, the costs of drug development are not covered by subsequent revenues [20]. Therefore, the interest of pharmaceutical companies in the approval of medicines for children is rather limited [20].

In order to include minors in studies an informed consent, depending on the country, of one or both parents and, if possible, of the child itself (assent) is required [21]. In many countries, there are recommendations as to when an assent should be obtained. The recommendations differ depending on the country. In Germany, an assent is recommended from the age of 7 years [22]. An assent is the consent of a child, who has not reached the age of consent to participate in a study, which is given after the child has been informed in an age-appropriate manner. Parents tend not to let their children participate in studies. Reasons for this can be, for example, the time required or the concern that the child's health could be adversely affected by the trial. Other reasons for refusing to participate in a study may include not being able to provide care for siblings or lack of family mobility [10, 23, 24]. In an outpatient setting, the presence of only one parent or guardian can be a further obstacle to participation in the study, as the consent from both parents might be required. Ineffective recruitment results in low sample sizes, so that no significant results can be achieved, and the recruitment period eventually has to be extended [10, 23, 24].

Furthermore, there are ethical reasons why studies on children were not common practice for a long time. Firstly, children up to a certain age are not able to consent. As indicated above, parents need to decide whether their child will participate in a study.

On the other hand, children, just like anyone else, have the right to health. In order to ensure this, studies need to be conducted [25, 26]. Since minors are the most vulnerable subgroup of the population, they also deserve special protection. As a result, laws and

recommendations have been introduced to protect children while integrating them into scientific studies (see 1.3).

1.2 Children's physiology

As mentioned previously, the dosage of pharmaceuticals in children is determined by body surface or weight. The dosage problem is exacerbated by differences in the physiology of children and adults, which will be outlined in the paragraphs below. At the International Conference for Harmonization (ICH) in 2000, the EMA (European Medicines Agency) defined categories, into which children could be assigned according to their age [27].

- Preterm newborn
- Newborn (0 - 28 days)
- Infant (28 days - 12 months)
- Toddler (13 months - 23 months)
- Preschool child (2 - 5 years)
- School age child (6 - 11 years)
- Adolescents (12 - 18 years)

This division into age groups is intended to group together children of a similar physiological developmental stage. It can be assumed that children of the same physiological stage of development metabolize drugs in a similar way.

The tissue concentration of a pharmaceutical is influenced by ADME (adsorption, distribution, metabolism, elimination) [5]. These factors differ in the pediatric population compared to the adult population.

There are different ways, in which drugs can be administered to children (e.g., oral, rectal, nasal, intravenous, inhalation, intraosseous, etc.). Therefore, developmental changes in the gastrointestinal tract, skin and lungs play a major role in the bioavailability of a drug. When a drug is administered orally, the pH of the gastrointestinal tract influences the stability of the drug. Newborns have a relatively high intragastric pH of >4 due to the lower total amount of gastric secretion and the lower acid production [28, 29]. The bioavailability of acid-labile drugs is therefore increased in the newborn period [30], the bioavailability of acid-containing drugs is reduced [31]. The bile is also subject to age-

related fluctuations [32, 33]. Transit time plays an important role in absorption as well. It increases in the first week of life due to higher gastric transit [34, 35]. Furthermore the intestinal motor activity matures over time [36, 37] .

Additionally, the condition of the intestinal surface cannot be ignored when evaluating absorption. While the intestinal surface decreases in the course of the life, the length of the intestine in children is increased in percentage compared to adult age [38]. The altered blood flow in the splanchnic area in the first two to three weeks of life can also influence the absorption rate [39-41]. In addition, there is a difference in enzyme activity between children and adults [42, 43]. Finally, the development of the intestinal flora also influences the age-dependent absorption [44]. Furthermore, the skin is better perfused during childhood [45, 46]. The intramuscular absorption rate may be reduced in newborns [47, 48]. Rectally administered agents have an increased absorption rate in infants because the liver is still very immature. A higher frequency of intestinal contractions increases excretion in infants and may therefore lead to reduced absorption of solid drugs [49-51].

The composition of the compartments changes in the course of life. Initially, the extracellular space contains predominantly water, which over time increasingly passes into the intracellular space. This has an influence on the distribution of pharmaceuticals in the physiological compartments [52]. Consequently, higher doses per kilogram body weight must be given to children in order to achieve a comparable plasma concentration of an active substance [53]. In infancy there are fewer plasma proteins such as albumin, which leads to an increased proportion of free active substance in the blood [54, 55]. The elevated presence of bilirubin and free fatty acids in the newborn period, which displace drugs from the binding sites to albumin, also results in a higher level of active substance in the blood [54-56]. The drug binding and distribution can be influenced by variability of blood flow, changes in acid-base balance and cardiac output [5]. The expression of transporters also has an influence on the distribution of drugs in the body [57, 58]. In addition, the permeability of the blood-brain barrier of newborns is higher than that of adults, so that drugs can pass through it more easily and reach the central nervous system [59].

Due to the incomplete maturation of the enzymes that metabolize active ingredients, drugs may be toxic to children [60, 61]. Therefore, dosage schemes for different age groups are necessary. Both, phase I enzymes, which are mainly responsible for oxidation, and phase

II enzymes, which are primarily responsible for conjugation, can be a reason for this [62, 63]. However, liver blood flow is increased in children compared to adults, because the liver is larger in relation to the total body size [64]. The bacterial colonization of the intestine also has an influence on the bioavailability of drugs [65-68].

The elimination of drugs primarily takes place via the kidneys. The maturation of the kidneys commences in the 9th week of pregnancy and lasts until early childhood [69]. During this time the blood circulation of the kidneys changes, as well as the glomerular filtration rate (GFR). At the age of 8 to 12 months GFR values of an adult are finally attained [70, 71]. Tubular secretion matures within the first year of life [70, 72]. Once again the dose should be adjusted to age, otherwise toxic concentrations of the administered drugs may result [73]. The lower urine pH in children also has an influence on the elimination of drugs. Acidic drugs are more likely to be reabsorbed [74].

1.3 Differences in pediatric versus adult clinical trials

1.3.1 Phases of clinical trials

Clinical trials for the approval of new medication consist of four phases (see Fig.1). The first phase is intended to provide an initial indication of the safety and pharmacokinetics of a novel active ingredient. Dose escalation and continuous evaluation of side effects may also be part of this phase. Only a few healthy volunteers are enrolled.

Phase II studies evaluate the efficacy and safety of a drug in a cohort of people suffering from the disease being targeted.

Phase III studies involve a large number of volunteers from all over the world. The new medication is now compared to the current standard therapy in a randomized controlled trial.

Phase IV studies take place after the licensing and market launch of a drug to test long-term efficacy and safety. Pediatric studies usually begin after completion of the second or third phase of clinical trials in adults. This has the advantage, that the data already collected on the safety and pharmacokinetics of the new medication in adults are available, so that they can be extrapolated to determine minimum and maximum doses in children [75]. Deviations from this procedure occur, for example, in the case of particularly severe diseases, conditions without available therapy or illnesses, that only

occur in children. In such cases, the pediatric clinical trial is already started in Phase I. An evaluation of the risk-benefit ratio should be conducted on a regular basis [23].

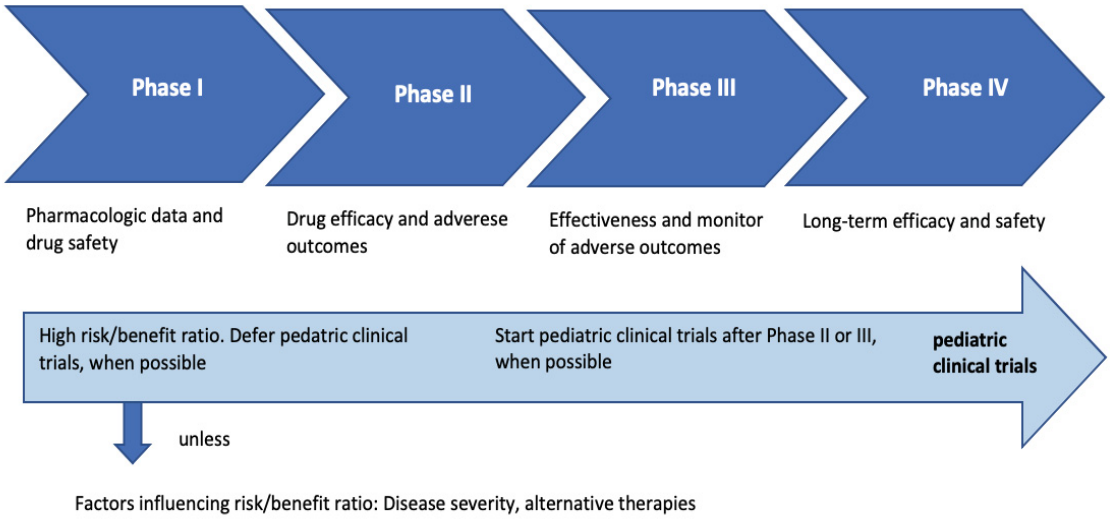

Fig 1: Phases of clinical trials

Modified from "*Phases of clinical trials*" [23]:

Phases of clinical trials in pediatric populations

1.3.2 Endpoints, recruitment and compensation

It is essential to define endpoints for studies in both adult and pediatric populations. The difference, however, is that parameters such as quality of life and pain may be difficult to assess depending on the age of the child [76]. Therefore, it is necessary to specify explicitly, how the respective endpoint is defined age-specifically, in the study protocol [77].

Some difficulties in recruiting participants in pediatric studies have already been mentioned above (see 1.1.2) and will be further amplified here. As the pediatric population is significantly smaller than the adult population, it takes more time to recruit the required number of patients [23, 78]. Some reasons for parental refusal to participate in studies have already been outlined before (see 1.1.2). On the other hand, reasons for participation may be a life-threatening condition of the child or the hope for a novel treatment [75, 79]. An accessible and understandable study information is more likely to motivate parents to let their child participate in a study [80]. Moreover partnership with pediatricians can be an important aspect in recruitment, as they are the ones, who can

scout possible probands [80]. Caldwell, P.H., P.N. Butow, and J.C. Craig found, that the reluctance of pediatricians to include patients in a study is an important factor in recruitment [81]. Reasons for this may be, for example, a feared deterioration in the doctor-patient relationship due to side effects. Another difference between trials in adults and children is the management of compensation of participants. It is common practice in adult research. In pediatric studies however, one should be careful with this, as a financial shortage of the parents should not be a reason for the child's participation in a study [82, 83]. Furthermore advertising of studies is less effective in the pediatric population [84].

1.3.3 Consent process

The informed consent includes a detailed explanation of the objective of the study, an explanation of the risks and potential benefits, information about alternative treatments, information about the research team, as well as potential compensation. It should also be pointed out, that a refusal to participate in the trial in no way affects the treatment of the patient [76, 85, 86]. A language, that is understandable to the subject or parental guardians, must be chosen and there should be room for questions. The study team member is responsible for ensuring that the information has been correctly understood. Young children are unable to consent due to their not yet entirely developed intellect and lack of legal capacity. Thus, for studies in the pediatric population the informed consent of the parent or guardian is required. Whether the consent of one or both parents is needed varies from country to country. In Austria and Belgium, for example, only one parent's signature is required, whereas in Germany both parents must provide written consent for study participation [22]. In addition, the child's informed consent/assent should be obtained, if possible (see 1.1.2). The research team member is responsible for assessing whether the child is already able to give consent. Should this be the case, the child will also sign a form. An attempt should be made to involve the child in the decision-making process and to provide the child with information that is appropriate for its age (see Fig.2) [76].

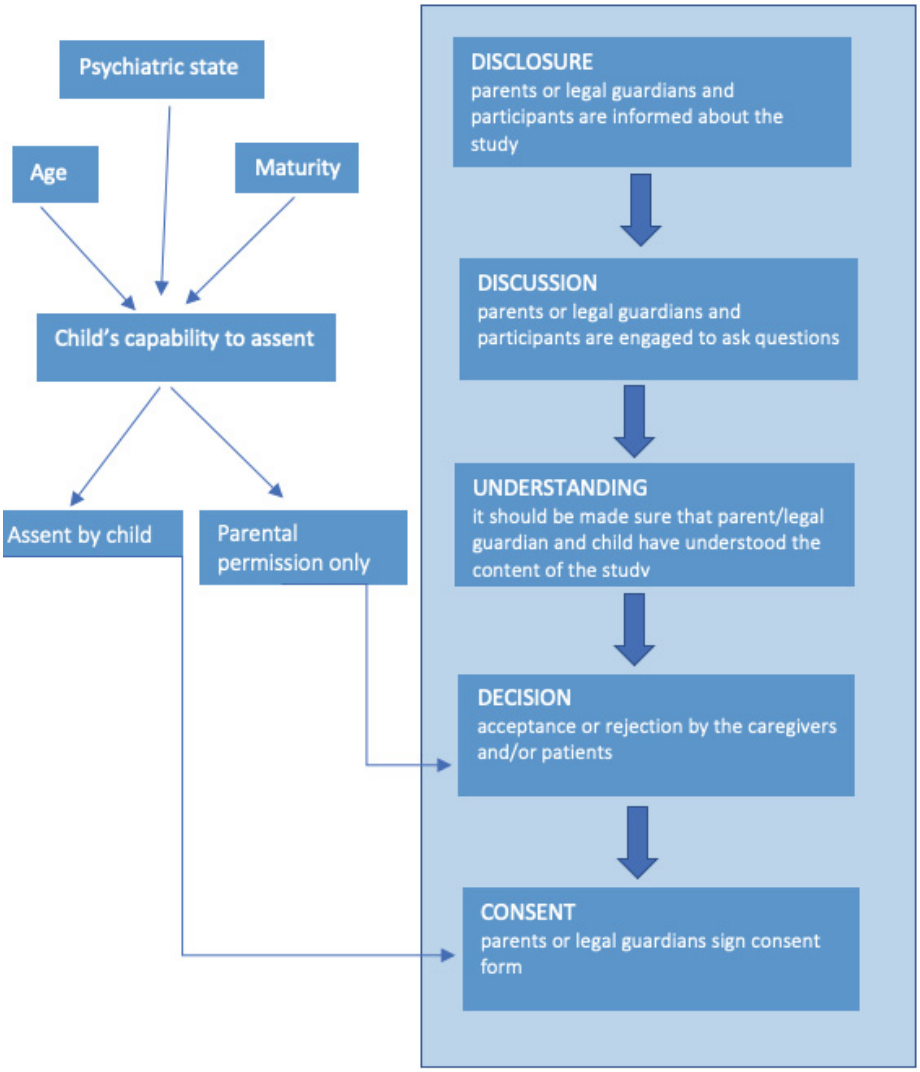

Fig. 2: Informed consent in pediatric clinical trials

Modified from "*Informed consent in paediatric clinical trials*" [23]:

Aspects influencing assent and consent in pediatric clinical trials

In pediatric studies, both the parent or guardian and the participant may terminate participation in the study early. However, this happens less frequently compared to studies in adults [87]. The reason for this could be, that children often go through a longer process before being included in a trial and that there are fewer therapy alternatives than in adults. The parents' commitment to the health of their child could also be a reason for the lower dropout rate [23].

1.4 Legislative

1.4.1 USA

For the reasons mentioned above, fewer registration studies were conducted for children, leading to a high rate of off-label or off-licensed prescriptions in childhood [7, 8]. Therefore in 1994 the *Pediatric Labeling Regulation* [88] was issued in the USA. According to this regulation, pharmaceutical companies should check, whether there is enough data to label the pediatric use of a drug. In order to print application information for children on the label, it had to be submitted to the FDA (Food and Drug Administration), which is responsible for drug development in minors [16, 84]. However, the *Pediatric Labeling Rule* was voluntary, so that only few well-conceived studies in children were conducted [87]. In 1997, the *FDA Modernization Act* and the *Pediatric Rule* have been passed, which came into force in 1998 [89]. Also, in 1998, the NIH (National Institute of Health) published a guideline decreeing the inclusion of children in research [88]. While the *Modernization Act* was intended to provide incentives to conduct pediatric studies by offering exclusivity or patent protection, the *Pediatric Rule* required RCTs (randomized controlled trials) to be performed before new therapies or indications in children were applied. In 2002, the *Best Pharmaceuticals for Children Act* was passed, which promises an extension of market exclusivity of patents for 6 months if the formulation has also been tested on children [89]. Unfortunately, it were mainly drugs that achieve high market share in adult medicine, that were tested in order to obtain patent protection for a further 6 months, even though these drugs had little relevance for the pediatric population [90, 91]. In October 2002 the *Pediatric Rule* was revoked by the court. The reason for that was, that the FDA had no authority to issue such decrees [90]. As a result, the *Pediatric Research Equity Act* was passed on November 19, 2003 [91]. Since then, the FDA has the authority to order pediatric studies for widely used drugs [89]. In 2007, the *Food and Drug Administration Amendments Act* (FDAAA) amended and reauthorized *PREA (Pediatric Research Equity Act)* and *BPCA (Best Pharmaceuticals for Children Act)* and extended them to October 2012 [89]. The *Pediatric Review Committee (PeRC)* has also been established. It is composed of experts with different backgrounds, who work together to ensure the quality of pediatric studies [89, 92]. Today, the two most important pillars for trials in children are the *BPCA* and the *PREA*.

1.4.2 EU

In 1997, an EMA (European Medicines Agency) round table was held to discuss the existing problems in pediatrics. In the following year, the *ICH (International Conference on Harmonisation)*, which was to harmonize the regulations of the EU, USA and Japan, adopted a guideline, that formed the basis of the European guideline *Note for guidance on clinical products in paediatric population (ICH Topic E11)* [93]. It was intended to promote the development of pediatric medical products internationally [94]. In December 2000, the EU Health Council called for similar steps to those already taken in the US with regard to studies in children [74]. A consultation paper entitled *Better medicines for children - proposed regulatory actions in paediatric medicinal products* was published by the European Commission in February 2002, "*which granted an extended patent for new medicines, data protection for paediatric medicines containing older active substances, and a network for paediatric studies*" [95]. The related *Reflection Paper* was adjusted in 2002 [94]. In May 2004, the *Directive (2001/20/EC)* [96] came into force, which was adopted in April 2001. It should ensure Good Clinical Practice in clinical trials. In the same year the first version of a *Regulation on medical products for paediatric use* was edited [97]. In addition, the German *Medicines Act* was amended in 2004 permitting the participation of children in placebo studies and improving the conditions for clinical studies involving minors [98]. In 2006, it was supplemented by the document *Ethical considerations in the conduct of clinical trials in children - Recommendations of the Ad Hoc Group on the development of implementing guidelines for Directive 2001/20/EC on good clinical practice in the conduct of clinical trials on medicinal products for human use*, which aimed in particular to ensure that the EU Member States dealt uniformly with ethical issues in clinical trials in children [94]. On 12th of December of the same year, the *Regulation for Medicinal Products for Children (No. 1901/2006)* of the European Parliament and Council was published and came into force in 2007 [99]. It obliges pharmaceutical companies to subject new drugs, whose indications also affect children to pediatric testing and, if necessary, to apply for marketing authorization for children [100]. A *Paediatric Investigation Plan (PIP)* must be submitted for each substance for which marketing authorization is applied. This should increase the rate of approved child-oriented drugs in Europe. Excepted from this are, for example, drugs whose indication area is irrelevant for children or if the approval for children results in a delay of the approval for other population groups. The *Paediatric Investigation Plans* are regulated

by the *Paedatric Committee (PDCO)* of the EMA [89], which is composed of one representative per EU member state [101]. Among others, representatives of the medical profession and patient organizations are represented. For an overview of which sub-specializations *PIP*s were submitted for from 2007 to 2015, see Figure 3. In the EU, pharmaceutical companies also receive a six-month extension of patent protection, if they conduct a study in the pediatric population. For non-patented active ingredients, the *PUMA (Paediatric Use Marketing Authorization)* gives pharmaceutical companies ten years of marketing protection, if a pediatric trial plan is applied [102]. In 2017, the EMA published a *10-year report* on the changes since the *Paediatric Drug Regulation* came into force [103]. Between 2007 and 2015, 238 new medicines and 39 child-appropriate dosage forms were authorized in the EU. 26% (89 out of 352) of approved medicines for pediatrics received marketing authorization following the introduction of the *Pediatric Regulation*. Recruitment of participants is still the biggest obstacle in pediatric studies (36% of reported difficulties in conducted *PIP* studies). By the end of 2015, 140 updates of product information and 16 new pediatric indications were approved. The proportion of studies involving minors rose from 9.3% in 2006 to 15% in 2013. It is also remarkable, that the number of newborns included in trials has increased from 470 in 2007-2009 to over 13,000 (25 times) in 2013-2015 [103]. Even previously neglected areas, such as pediatric rheumatology, now received long-awaited marketing authorizations for medications [104]. In October 2018, an action plan, jointly developed by the EMA and EC (European Commission), was presented. It was intended to address the insufficiencies noted in the *ten-year report*. A re-evaluation took place in December 2020. Many of the set objectives have already been met, some are still in progress [105].

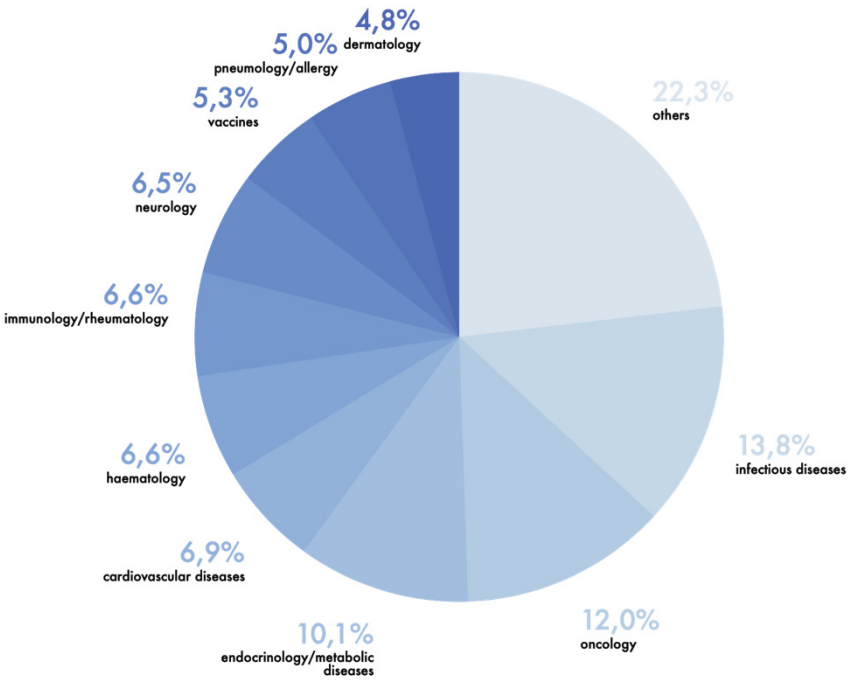

Fig 3: Therapeutic areas addressed by the pediatric investigation plans

Modified from "*therapeutic areas addressed by the paediatric investigation plans (2007-2015) based on EMA database*" [106]

1.5 Pediatric galenic formulations

In 2006's *Reflection paper: Formulations of choice for the paediatric population* EMA states: "*There is only limited knowledge available on the acceptability of different dosage forms, administration volumes, dosage form size, taste, and importantly, the acceptability and safety of formulation excipients in relation to the age and development status of the child* [107]." Furthermore, they emphasize that "*many medicinal products are not currently available in formulations suitable for administration to the pediatric population. Consequently, healthcare professionals frequently resort to the preparation and administration of unlicensed formulations by manipulation of adult dosage forms* [107]."

According to the EMA, there are numerous criteria, on which effective drug administration and the optimal dosage form depend. Those are mentioned below [107].

- Capability: Age, physiological and psychological development are relevant factors when it comes to administration of drugs.
- Illness: Depending on whether it is an acute or long-term disease, the administration of medication is influenced. In cases of acute pain or discomfort, it occurs, that children refuse to take the medication. In chronic diseases, however, children are often accustomed to taking medication.
- Parent/Caregiver: The person administering the drug also has an effect on the reaction of the child.
- Disability: Children with disabilities partly receive their medication through feeding tubes. In some cases, medications must be crushed and/ or dissolved in order to be administered via feeding tube. This can lead to interactions with the food administered. In addition, some of these children cannot communicate side effects, that may occur.
- Culture: Cultural differences in the preferred route of administration, as well as differences in taste, should be taken into account.

1.5.1 Basic criteria for pediatric drug formulation

According to Krause and Breitkreutz [108] pediatric drug formulation should provide:

- "*Sufficient bioavailability*
- *Safe excipients*
- *Palatable and /or acceptable properties*
- *Acceptable dose uniformity*
- *Easy and safe administration*
- *Sociocultural acceptability*
- *Precise and clear product information*
- *Parent/caregiver friendly*" [108]

The EMA defines the ideal dosage form in its *Reflection Paper* of 2006 [107] as

- "*One dosage form fitting the full range of children,*
- *Having a minimum of or only non-toxic excipients,*
- *Being easily produced, elegant and stable*" [107]

1.5.2 Advantages and disadvantages of currently used formulations in pediatrics

There are several different dosage forms on the market. This is an advantage, as it can be varied by personal preference and tolerance. Oral dosage forms, especially liquids in younger infants and tablets in older children, are most commonly used in pediatrics [109]. There are several issues with the currently available pharmaceutical forms, some of which are outlined in the following.

1.5.2.1 Liquid formulations

The advantage of liquid dosage forms, such as aqueous solutions, suspensions, emulsions and syrups, is, that different dosages can be measured and administered. A measuring instrument should always be included in the package. However, it should be noted, that large quantities of liquid are often not accepted. If runlets or spitting out of the administered medication occur, underdosing may result. If medication is given after expectoration, overdoses may take place. EMA states in 2011's *Draft Guideline on Pharmaceutical Development of Medicines for Paediatric Use*: "*For oral liquid solutions and dispersions, the maximum recommended single dosing volume is 5 ml for children aged below 4 years and 10 ml for children aged between 4 and 12 years. The minimum dosing volume will be determined by the accuracy of the dosing device*" [110]. For a long time, liquid dosage forms were preferred for children under 6 years of age, as it was assumed that they were not yet able to swallow tablets [107]. In 2006's paper, EMA points out "*suspensions may be very useful for formulation of substances with poor taste characteristics; as by minimizing the amount of drug in solution, the palatability of the formulation can be improved. Also, suspensions can facilitate higher drug loading than solutions and hence can reduce the dose volume. Suspensions containing coated pellets, or ion exchange resins may be useful to modify drug release*" [107]. A suspension must be mixed properly before use, otherwise over- or under-dosing may occur. Solutions should be preferred, as they are associated with higher acceptability. Concerning any liquid formulation, the WHO mentions in 2010's paper "*Development of paediatric medicines: points to consider in pharmaceutical development"*: "*The need for using stabilizing agents, e.g., antimicrobial preservatives, is a major drawback as is the potential chemical instability, which may require controlled storage conditions during*

distribution and use. Oral liquid preparations are less transportable than solid-dose preparations because of the relative high bulk volume" [109].

Liquid dosage forms therefore are mainly suitable for first-world countries and less optimal for third-world countries [111].

1.5.2.2 Solid formulations

The main concern with oral formulations, especially in young children, is children's ability to swallow solid formulations regarding the risk of inhalation and aspiration. Already in 2006, the EMA had recognized that "*solid oral dosage forms, such as tablets and capsules can offer advantages of greater stability, accuracy of dosing and improved portability over liquid formulations. Formulation taste is rarely an issue, with film and/or sugar coats used to improve palatability [107].*" But out of concern about the swallowability of tablets in young children, syrup remained the gold standard. In 2010, the WHO pointed out, that this concern was not based on scientific data [109], after they had already recommended a paradigm shift from liquid to solid dosage forms as result of an expert meeting on pediatric dosage forms in 2008 [111].

WHO states "*It has been thought generally that even small tablets and capsules to be taken as whole are not acceptable below the age of six years. However, no good scientific evidence exists. Recent preliminary evidence indicates that mini-tablets (e.g. 2-3 mm) may be acceptable even for small children (2–4 years old)*" [109]. While the WHO describes in its paper the individuality in acceptability depending on the child, in its draft guideline from 2011, EMA indicates precise age limits for certain sizes of tablets. They state, that "*the tablet size is fundamental to the ability of a child to swallow a tablet. Young children may be able to accept small tablets, but not large tablets. Unless otherwise justified by appropriate studies or clinical evidence, small tablets (i.e. tablets from 3 to 5 mm diameter, width or length whichever is the longest) will not be considered acceptable for children below the age of 2 years, medium sized tablets (i.e. tablets from 5 to 10 mm) for children below the age 6 years, large tablets (i.e. tablets from 10 to 15 mm) for children below the age of 12 years and very large tablets (i.e. tablets from 15 mm) for children below the age of 18 years*" [110]. In its final guideline of 2013, however, the EMA revises these age limits and also highlights the lack of clinical studies. "*It should be noted, that limited data is available in the literature regarding the influence of size,*

shape and the number of tablets on acceptability in different paediatric age groups" [112].

1.6 Mini-tablets

Tablets are the most commonly used formulation in adults. However, it is not recommended to divide them up to create appropriate dosages and swallowable sizes for pediatric patients [14]. Mini-tablets could be a solution for this problem. There is no official definition of mini-tablets, only in literature they are defined as tablets with a diameter of up to 3.0 mm [113]. Since mini-tablets are often difficult to handle due to their size, various devices have been developed for application assistance, with the help of which the required number can be counted more easily [114].

There are uncoated and coated mini-tablets. Uncoated mini-tablets have a lower risk of choking, because they dissolve slowly when they are exposed to saliva. Therefore, they are mainly used in infants and neonates [115]. A disadvantage of uncoated mini-tablets is, that unpleasant taste of an API (active pharmaceutical ingredient) may reduce compliance.

Herein lies the advantage of the coated mini-tablet, where taste masking can hide unpleasant taste [116]. In addition, coated mini-tablets have the benefit, that the drug and the gastrointestinal tract can be protected against premature release [117]. Furthermore, Lajonie et. al were able to demonstrate cost savings by replacing liquid dosage forms with solid dosage forms [118].

1.6.1 Previous research

Several studies on the acceptability and swallowability of mini-tablets in different shapes have already been conducted. The majority of them have been published by the research group Klingmann et al. and will be discussed in a separate section. In 2009, Thomson et al. [119] conducted the first prospective uncontrolled, single-dose study with mini-tablets in infancy. 100 children between 2 and 6 years of age each received one uncoated drug-free mini-tablet of 3 mm diameter. A distinction was made between swallowed and non-swallowed, whereby chewed, spat out and refused were summarized under the latter. They observed a large difference between the age groups. Children between 4 and 6 years swallowed the mini-tablets in 76-87%, while children between 2 and 4 years were

frequently chewing the mini-tablets. No choking occurred. Thomson et al. concluded that the administration of mini-tablets between 2 and 6 years was safe. 2013, Van Riet-Nales et al. [120] compared four oral dosage forms without active ingredient in 143 children between 1 and 4 years of age in terms of acceptability. Acceptability was evaluated by the parents, who filled out a questionnaire after administration. Tablets of 4 mm diameter, a suspension, a powder and syrup were evaluated. The mini-tablets showed the highest VAS-score (visual analogue scale), which is a method, in which the subjective perception should be given on a scale of 1 to 10 or 0% to 100%. Van de Vijver et al. [121] conducted a study with 16 children with cystic fibrosis between 6 and 30 months of age, in which pancreatic lipase was given in 1 to 4 mini-tablets of 2 mm diameter for 5 days. The second objective of this study was to evaluate the palatability of the mini-tablets, which was described as "*fair to good*". Kluk et al. [122] finally found that children between 2 and 3 years of age can also swallow multiple mini-tablets of 2 mm or 3 mm diameter in fruity jelly, whereby neither the number of mini-tablets (between 5 and 10) nor the size of the mini-tablets (2 mm or 3 mm diameter) showed a significant impact. Furthermore, Ansah et al. [123] showed, that the adherence is higher when parents or caregivers administer mini-tablets than when they administer syrup. In October 2020 Bracken et al. conducted a clinical trial, during which children aged 4-12 years swallowed round placebo tablets (6 mm, 8 mm and 10 mm diameter), smallest to largest. The water used to swallow the tablet, as well as the facial expressions and behaviors were observed. On top of that, the participants filled out a questionnaire on acceptability and swallowability of the tablets. The majority of the children successfully swallowed the tablets. Swallowability was found to be inversely associated with tablet size. Only 67% of the children included in the trial were able to swallow the 6 mm tablet, 91% the 8 mm sized tablet and 95% the tablet with 10 mm diameter. [124].

As far as we are aware to date there are no clinical studies on the acceptability of oblong tablets in childhood.

1.6.3 Previous trials of the study group

The Clinic for General Pediatrics, Pediatric Cardiology and Neonatology at the University Hospital Düsseldorf has conducted several studies on the acceptability and swallowability of mini-tablets in children. A pilot study by Spomer et al. [125], conducted in 2010 compared acceptability and swallowability of uncoated mini-tablets of 2 mm diameter with 3 ml glucose syrup in 60 inpatients or outpatients between 6 months and 6 years of age. It was shown that the acceptability of the mini-tablets was higher or as good as the acceptability of the syrup. In 2013, Klingmann et al. [126] compared a larger patient population of 306 children in the same age groups with regard to acceptability of drug-free coated mini-tablets with a diameter of 2 mm drug-free uncoated mini-tablets with a diameter of 2 mm, and 3 ml glucose syrup. In this confirmatory study, the acceptability of the mini-tablets exceeded the one of the syrup. In 2015, Klingmann et al. [127] compared the acceptability and swallowability of 0.5 ml glucose syrup and uncoated mini-tablet with 2 mm diameter in 151 newborns. Both dosage forms were accepted by all participants. However, the swallowability of the mini-tablet significantly exceeded that of the syrup. The acceptability and swallowability of several drug-free mini-tablets compared to an equivalent amount of syrup in children between 6 months and 6 years of age was investigated by Klingmann et al. [128] and published in 2018. The children were divided into two age groups (6-23 months and 2-5 years). The study showed, that >/= 25 mini-tablets were better accepted in children over 6 months than an equivalent dose of syrup. Children older than 2 years tolerated </= 400 mini-tablets better than the equivalent syrup dose. Furthermore, the acceptability, swallowability and palatability of orodispersible films (ODF) in children under 1 year of age compared to syrup was investigated [129]. The study revealed a superiority of ODFs compared to syrup in terms of acceptability and swallowability. The palatability was also favorable for ODFs.

In all these studies, the evaluation criteria established and validated by Klingmann et al. were used (everything swallowed, chewed/partially swallowed, spat out, choked on/swallowed the wrong way). In the current study palatability was rated as pleasant, no change or unpleasant.

1.7 Oblong tablets: Objectives of this thesis

In consideration of the disadvantages of liquid dosage forms described in 1.5.2.1, it is necessary to develop new solid dosage forms for children, to test their acceptability, swallowability and palatability and to compare it to the gold standard syrup, as well as to the newly recommended mini-tablets.

One disadvantage of the mini-tablets, however, is the limited amount of API they can be loaded with. Thus, if larger doses are needed, an alternative is required.

In adults and elderly patients, it was shown, that the acceptability of oblong tablets was higher compared to round tablets [130, 131]. For children, there are no findings in this regard so far [132].
The study this dissertation refers to tested one drug-free oblong tablet (2.5 mm x 6 mm) in comparison to 3 drug-free mini-tablets (2 mm diameter) and 3 ml glucose syrup, which corresponds to an equivalent dose of possible active ingredient.

It is the first study on acceptability, swallowability and palatability of oblong tablets in infancy. It is thus investigating a further pharmaceutical formula, which will extend the range of possible formulations in pediatrics.

The study has received a positive opinion by "*Ethikkommission der Heinrich-Heine-Universität Düsseldorf*" (study number: 2018-74-KFogU).

Inpatients and outpatients were recruited as participants between 15.10.2018 and 18.12.2018 in the Department of General Pediatrics, Neonatology and Pediatric Cardiology, University Children´s Hospital, University Clinic Düsseldorf (UKD), Düsseldorf, Germany.

Primary Objectives

- To demonstrate non-inferiority in acceptability of the oblong tablet in comparison to 3 ml glucose syrup in children aged between 1 year and 5 years inclusive.

Secondary Objectives

- To demonstrate non-inferiority in acceptability of the oblong tablet in comparison to three mini-tablets in children aged between 1 year and 5 years inclusive.
- To compare swallowability of the oblong tablet and of 3 ml glucose syrup in children aged between 1 year and 5 years inclusive.
- To compare swallowability of the oblong tablet and of three mini-tablets in children aged between 1 year and 5 years inclusive.
- To compare acceptability of an oblong tablet and of 3 ml glucose syrup in subsets of children aged 1 to 2 years, 2 to 3 years, 3 to 4 years, 4 to 5 years and 5 to 6 years.
- To compare acceptability of an oblong tablet and of three mini-tablets in subsets of children aged 1 to 2 years, 2 to 3 years, 3 to 4 years, 4 to 5 years and 5 to 6 years.
- To compare swallowability of an oblong tablet and of 3 ml glucose syrup in subsets of children aged 1 to 2 years, 2 to 3 years, 3 to 4 years,4 to 5 years and 5 to 6 years.
- To compare swallowability of an oblong tablet and of three mini-tablets in subsets of children aged 1 to 2 years, 2 to 3 years, 3 to 4 years, 4 to 5 years and 5 to 6 years.
- To compare the palatability of an oblong tablet, three mini-tablets and 3 ml syrup in each age group.
- To identify any possible problem that could occur during deglutition.
- To identify the percentage of children who inhaled or coughed during ingestion of any of the oral placebo formulations.
- To investigate the safety of the oral placebo formulations.
- To investigate the percentage of approached parents consenting to participation of their child in this study.
- To identify reasons why approached parents are not willing to agree to the participation of their child in this study.

2 “*Acceptability of small-sized oblong tablets in comparison to syrup and mini-tablets in infants and toddlers: A randomized controlled trial*”

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Acceptability of small-sized oblong tablets in comparison to syrup and mini-tablets in infants and toddlers: A randomized controlled trial

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ABSTRACT

Objective: There is limited evidence for the acceptability of various drug formulations holding the potential to improve medicines administration to children. Suitable formulations need to meet the requirements of pediatric patients. Previous studies have demonstrated the acceptance of mini-tablets. Oblong tablets may carry more active ingredient content per unit than mini-tablets and could be an important alternative when the drug substance requires administration of higher doses.
The primary objective was to demonstrate non-inferiority of acceptability of oblong tablets in comparison to 3 ml glucose syrup in children aged 1 to 5 years. Secondary objectives were investigation of acceptability, swallowability and palatability of mini-tablets, oblong tablets and glucose syrup in children between 1 and 5 years.
Methods: An open, randomized, single dose two-way cross-over design in two parallel study arms was applied. 280 children were stratified to one of five age groups and randomized to receiving one oblong tablet (2.5 × 6 mm) in comparison either to 3 ml glucose syrup or to three mini-tablets (2 × 2 mm). Acceptability and swallowability were assessed according to pre-defined evaluation criteria. The application of the formulations was video documented to evaluate the palatability.
Results: As primary objective, non-inferiority was observed regarding acceptability of the oblong tablet compared to syrup in all age groups (84.4% vs 80.1%, difference 4,29% points with 95% CI of −3.00%,11.57%). For swallowability, superiority of the oblong tablet compared to syrup could be shown (74.5% vs. 53.2%, difference 21.26% points, 95% CI of 11.29%, 31.23%). Regarding palatability, <10% of children demonstrated unpleasant reaction after intake of the oblong tablet or mini-tablets as graded by both raters, however, in contrast up to 40% of children after intake of syrup.
Conclusion: Oblong tablets are a promising, safe alternative to liquid drug formulations and administration of multiple mini-tablets in children.

1. Introduction

Adult and pediatric patients are different with respect to swallowing abilities, taste preferences and therefore, different dosage forms are required for reliable medical oral treatment of patients of different age groups [1]. Within the heterogeneous pediatric patient cohort, which ranges from neonates to adolescents, different dosage forms for the various needs and conditions in the respective age groups may be required [2]. The properties and required amount of active substance per dosing unit request the availability of a range of formulation options. Despite the importance of suitable formulations in pediatric pharmacotherapy, there are few proven facts about the use of dosage forms in current practice [3]. Still, more than 30% of drugs for children have either no pediatric marketing authorization at all [4] or are prescribed off-label [5]. This is due to the fact that pivotal marketing authorization studies are generally conducted in adults and not in children, which may

Abbreviations: CI, Confidence interval; DRKS, German Clinical Trials Register; EMA, European Medicines Agency; GMP, Good Manufacturing Practice; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

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result in inadequate doses and substances being administered to pediatric patients [6]. That leads to a higher risk of possibly inadequate treatment or side effects and deprives children of the full benefit of therapeutic progress.

The current clinical practice of administering liquids or syrups to children results in a surprisingly unreliable dosing with substantial under- or over-dosage [7]. Thus, it is not only necessary to investigate the efficacy and optimal doses of pharmaceutical substances for different pediatric age groups, but also to develop child-friendly galenic formulations for the most suitable routes of administration. In clinical practice, suitable oral treatments for children of different age and physical development stages need different conditions: availability of the required dose strength, the child's ability to take sized solid oral dosage forms, and their acceptability. Yet, this often leads to the commonly poor choice of an alternative formulation such as liquid or suppository. Despite the importance of suitable formulations in pediatric pharmacotherapy, there are few proven facts about the use of dosage forms in current practice [3]. The understanding of the children's ability to swallow orally administered solids often seems to be based more on perception rather than evidence [8]. Acceptability, swallowability and palatability have proven to be appropriate parameters to objectively assess the suitability of oral formulations for children and to allow the provision of recommendations for the best suited oral pediatric formulations for the respective age group [8–13].

The 2006 EMA reflection paper "Formulations of Choice for Pediatric Population" [3] did not only provide an overview of the state of knowledge on pediatric formulations, but also concluded that there may not be a single formulation ideal for all ages of childhood and adolescence. Suitable tablets would meet targets: a) one dosage form fitting the full range of children, b) a minimum of or only non-toxic excipients, and c) easily produced, elegant, stable drug formulations. Furthermore, the EMA recommended the development of new oral pediatric formulations, based among others on tablets and orodispersible dosage forms [3].

Therefore, scientifically based data are needed to compare different oral pediatric routes of administration that relate to the suitability and ability of children (especially at an early age) to incorporate different galenic formulations in order to increase the safety and reliability of drug administration. In pediatric practice, syrup is the most commonly used formulation. In addition, specially developed mini-tablets have advantages as they are easy to use and an inexpensive alternative. They also offer advantages over liquid formulations in terms of drug stability, potentially toxic excipients and storage conditions. The suitability of mini-tablets with a diameter of 3 mm in 5-year-old children has been demonstrated, while less than half of pre-school children were able to swallow them [8].

In several previous studies of our working group, we were able to demonstrate the acceptability and swallowability of single and multiple even smaller mini-tablets with a diameter of 2 mm in children aged between 2 days and 6 years [9–13]. In light of these findings, the revised version of the EMA guideline of 2014 [14] did no longer contain an age recommendation for solid oral dosage forms. In this guidance mini-tablets were only mentioned as a multiparticular dosage form comprising multiple drug carriers per single dose. However, most recently a medical product has been introduced to the market with a single mini-tablet containing the pediatric single dose of melatonin. Another orodispersible mini-tablet containing enalapril is currently under development [15,16]. However, mini-tablets cannot always be used as they can be loaded by max. 2.5 mg. Taking into consideration the above results, it was now time to develop a formulation that may deliver higher doses of active substance in a more condensed form such as an oblong tablet. It has been shown in adults and elderly patients that oblong tablets may be superior regarding acceptability if compared to round tablets [17,18]. In children oblong tablets have not been investigated systematically so far in order to demonstrate the advantages and the suitability of an oblong tablet [19]. This clinical trial was performed to identify how tablet geometry of an oblong tablet affects acceptability in children.

2. Objectives

The primary objective of this study was to demonstrate non-inferiority in acceptability of an oblong tablet compared to 3 ml of glucose syrup in children between 1 and 5 years inclusive.

Secondary objectives of this trial were comparison of acceptability, swallowability and palatability in subsets of children aged 1 to 2 years, 3 to 4 years, 4 to 5 years as well as 5 to 6 years.

Possible problems occurring during deglutition and the percentage of children who inhaled or coughed during ingestion of any oral placebo form were assessed.

Furthermore, the percentage of approached versus consenting parents was analyzed. For those parents who did not want to participate, the reason for non-consenting was recorded.

3. Methods

3.1. Design

The trial was conducted in two parallel study arms in a single-center, open, randomized, single-dose, two-way cross-over design with age stratification in five groups. Randomization was performed within each age group. Children in study arm A received a placebo oblong tablet and 3 ml glucose syrup in randomized order, in study arm B, one oblong tablet and three 2 mm placebo mini-tablets. The Ethics Committee of the Medical Faculty of the Heinrich-Heine-University Düsseldorf gave a favorable opinion for the study (No. 2018-74-KFogU). The study was registered in the German Clinical Trial Register (No. DRKS00014341). It was conducted according to the E6 Guideline of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) on "Good Clinical Practice" with a risk-adjusted monitoring level and adequate insurance cover. As the study medication did not contain any active substance, the trial did not fall under the German drug law and was thus not subject to competent authority approval.

3.2. Study population

The parents of 358 children, aged between 1 and 5 years inclusively, were approached, 283 parents (79%) consented and thus sufficient pediatric patients were enrolled to achieve 280 evaluable patients in two study arms (141 children in study arm A and 139 children in study arm B, each study arm divided into 5 age sub-groups) that complied with the in-/exclusion criteria. The recruitment took place between October 15th, 2018 and December 18th, 2018 at the Department of General Pediatrics, Neonatology and Pediatric Cardiology, University Hospital Düsseldorf, Germany.

An informed consent signed by both parents and, if possible, an attempting an assent from the child, was mandatory before starting any study related procedures. Apart from the defined age other inclusion criteria had to be met, namely being able to swallow, as well as parents and children understanding the course of the study. Exclusion criteria were any impairment of swallowing as a result of chronic or acute illness or oral deformation, family history of lactose intolerance, pre- and concomitant medication causing nausea, fatigue or paralysis, and patients shortly after surgery.

3.3. Drug formulations

All formulations were free of active ingredients.

Both, the mini-tablets with a diameter of 2 mm and the oblong tablets (2.5 × 6 mm; one oblong tablet has approximately the size of three mini-tablets) (Fig. 1) were produced by NextPharma in their sites Pharbil Waltrop, Waltrop, Germany (mini-tablets) and allphamed

Fig. 1. Oblong tablet (2.5 × 6 mm) in comparison to mini-tablets (diameter 2 mm) and a 1 Euro coin.

Pharbil, Göttingen, Germany (oblong tablets in accordance with Good Manufacturing Practice (GMP). Both contained the same pharmaceutical ingredients: Lactose monohydrat, microcrystalline cellulose, magnesium stearate and anhydrous colloidal silica.

The glucose syrup was manufactured by Caesar & Loretz, Hilden, Germany, and was diluted with boiled tap water to a 15% glucose syrup at the trial facility prior to use.

3.4. Administration of formulation and assessment

Patients fulfilling all in- and exclusion criteria were randomized to their study arm and order of application. After inspection of the oral cavity children received the first formulation. The tablets were placed in the child́s mouth. The syrup was administered with a syringe. To facilitate swallowing the children were offered a drink of choice.

The process of deglutition was permanently monitored and the children's reactions were video-documented for subsequent evaluation. After swallowing, the oral cavity was again examined to identify residues of the formulations.

The same procedure was repeated with the second formulation as soon as the child was ready and within 15 min.

3.5. Evaluation criteria

The evaluation criteria for the swallowing of the three formulations are depicted in Table 1.

Acceptability was defined as a combination of the first two evaluation criteria ("everything swallowed" and "chewed / partially swallowed"). Swallowability was defined as the first evaluation criterion ("everything swallowed") only with no chewing or no residuals found during oral inspection.

The palatability was video documented and evaluated independently by two blinded raters according to the following criteria presented in Table 2.

3.6. Statistical methods

The sample size required to meet the primary objective (demonstration of non-inferiority in acceptability of the oblong tablet in comparison to glucose syrup) was based on an 80% syrup acceptability rate as observed in previous clinical trials [9,11–13]. The non-inferiority margin was defined as 15%-pts. Setting the significance level to 2.5% (one-sided) and the power to 90%, the sample calculation resulted in a total of 132 evaluable cases for this study arm (assuming a correlation of 0.3 between the two arms) based on the sample size formula of Liu et al. [15]. Since this study was stratified into 5 age groups, and each age group was to be balanced by treatment sequence, 140 children were to be randomized (i.e., targeting at 28 children per age group). With regard to the secondary objective (demonstration of non-inferiority of acceptability of the oblong tablet in comparison to three mini-tablets), the acceptability rate of the mini-tablets was expected to be higher than 80% (up to 90%) thus leading to a smaller required sample size for this study arm. However, the same sample size of 140 children was chosen as in the other study arm to get similarly precise estimates of the acceptability rates.

The binary primary endpoint "acceptability" in children aged 1 year to < 6 years was analyzed by applying the analysis proposed by Schouten and Kester (2010) [16]. First, the difference between the acceptability rates of the oblong tablet and the reference product was estimated for each sequence group and then, in a second step, averaged over both sequence groups. For the averaged difference of the acceptability rates, corresponding one-sided 97.5% confidence intervals were calculated. The oblong tablet was considered as non-inferior in comparison to the reference product, if the lower limit of the one-sided 97.5% confidence interval for the averaged difference in acceptability rates [r(Oblong tablet) – r(Reference)] exceeded −15%-pts. The corresponding hypotheses to be tested were: H0: π(Oblong tablet) $\leq$ π(Reference) – 15% versus H1: π(Oblong tablet) > π(Reference) – 15%, where π denoted the true rate for acceptability. Superiority testing was permitted in a second step when non-inferiority had been demonstrated.

The secondary outcomes of swallowability and palatability were also analyzed as binary outcome and the analyses were performed analogously to the analysis of acceptability. The degree of agreement between

Table 1
Evaluation criteria for acceptability and swallowability of oblong tablets, mini-tablets and syrup.

Criteria	Oblong tablet and Mini-tablets	Glucose Syrup
1	Everything swallowed: which implies that no chewing took place during deglutition and no residuals of the solids were found during oral inspection	Everything swallowed: which means that no liquid was left in the mouth and no drops left the mouth
2	Chewed: which implies that chewing was observed before deglutition or that the whole or parts of the solids were found during oral inspection	Partially swallowed: which means that the child did not swallow completely and that there was a leftover of the syrup in the syringe or in the mouth
3	Spat out: which means that no deglutition took place and that the solids were no longer in the child's mouth	Spat out: which means that no deglutition took place because the child disgorged the glucose syrup directly
4	Chocked on: which means that the solid was swallowed the wrong way or that a cough was caused	Swallowed the wrong way: which means that the syrup was swallowed the wrong way or that a cough was caused
5	Refused to take: which implies that the child didn't allow the investigator to place the solids in the mouth	Refused to take: which implies that the child didn't allow the investigator to place the syringe in the mouth or that the child didn't close the mouth correctly and that all glucose syrup was leaking out of the mouth because no deglutition took place

Table 2
Evaluation criteria for the palatability of oblong tablet, mini-tablets and syrup based on video documentation

	Criterion		Interpretation
①	Pleasant	Positive hedonic pattern	Tongue protrusion, smack of mouth and lips, finger sucking, corner elevation
②	No change	Neutral	Neutral mouth movements (irregular and involving lips)
③	Unpleasant	Negative aversive pattern	gape, nose wrinkle, eye squinch, frown, grimace, head shake, arm flail

two raters concerning palatability was quantified by Cramer's V (calculated from the underlying 3x3 contingency table).

4. Results

4.1. Demographic data

79% of approached parents agreed to participate. The highest refusal rate was found in age group 2, where 21 guardians (5.9%) declined to participate. The lowest refusal rate was in age group 3, where only 8 guardians (2.2%) rejected participation. The main reason for non-participation was the unavailability of the second parent for informed consent. The second most frequent reason was refusal by the mother, the father or both parents because of a lack of interest in participating in a clinical trial. A language barrier was also a frequent reason for non-participation.

4.1.1. Oblong tablet vs. syrup (study arm A)

One hundred and forty-two children were randomized and received the study medications in both periods in arm A. Of these, 70 (49.3%) were randomized in the treatment sequence of Oblong tablet followed by syrup and 72 (50.7%) in reverse order. All 142 children met all inclusion criteria and did not meet any exclusion criterion. However, one child was excluded from the analyses because a randomization error occurred. Thus, there were 141 children who were valid for evaluation in the per-protocol set. Randomization was divided into 5 age groups according to the age of the children. About 30% of the children were female and 70% were male in the treatment sequence oblong vs. syrup, while 45% were female and 55% male in the other treatment sequence.

4.1.2. Oblong vs. mini-tablet (study arm B)

One hundred forty-one children were randomized and exposed to study medication in arm B in both periods. Of these, 70 (49.6%) were randomized into the treatment sequence of oblong tablet followed by mini-tablet and 71 (50.4%) into the treatment sequence mini tablet followed by oblong tablet. All 141 children met all inclusion criteria and did not meet any exclusion criteria. One child, however, was excluded from the analysis because a randomization number was mistakenly assigned that had already been used for another child. Another child was excluded because it was randomized to the wrong age group. Altogether, there were 139 children valid for evaluation in the Per-Protocol Set. About 45% of the children were female and 55% were male in the treatment sequence oblong tablet versus mini-tablet, and likewise 50% female and 50% male children participated in the other treatment sequence.

4.2. Administration of formulations

In 90% in both study arms and across almost all age groups the most frequently used swallowing vehicle was water. The remaining children received milk, tea, fruit juice or lemonade.

4.3. Acceptability

The primary outcome of acceptability was analyzed as binary outcome by combining the first two evaluation criteria ("everything *swallowed" and "chewed"* for the tablets or "*everything swallowed" and "partially swallowed"* for syrup, respectively) as "accepted" and the three remaining evaluation criteria as "not accepted".

4.3.1. Oblong tablet vs. syrup (study arm A)

The overall acceptability rate of the oblong tablet was 119 / 141 (84.4%) and the total acceptability rate of the syrup 113 / 141 (80.1%) (Fig. 2A). This resulted in a difference of 4.29 percentage points at a 95% confidence interval (CI) of: (-3.00%, 11.57%). The non-inferiority of the oblong tablet compared to syrup was clearly demonstrated, while the superiority of the oblong tablet in comparison to syrup could not be demonstrated.

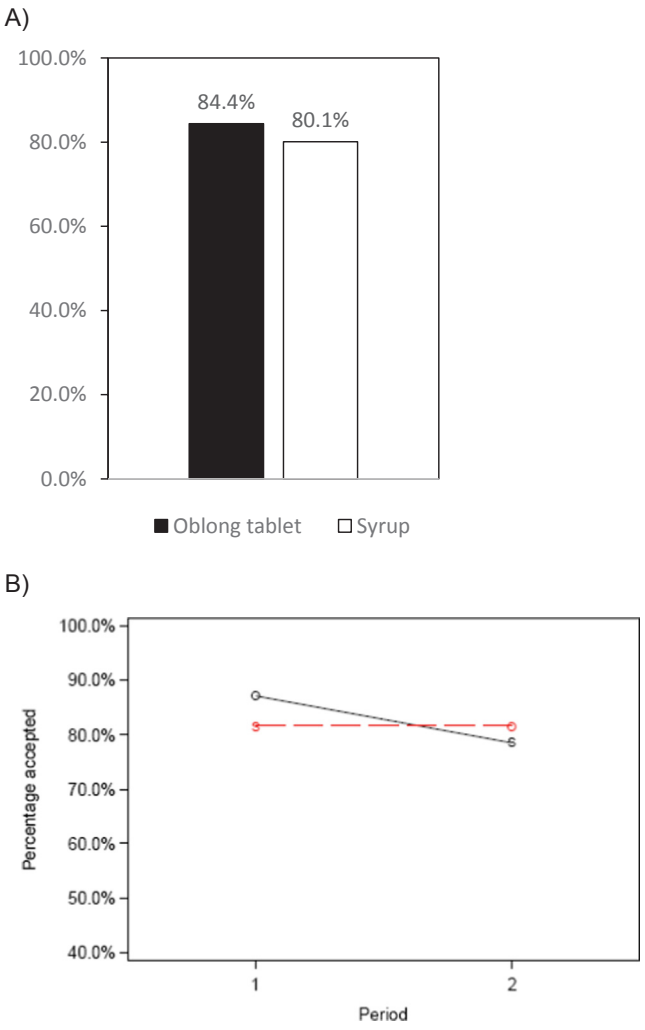

Fig. 2. Acceptability of oblong tablet in comparison to syrup. (A) Overall age groups (B) Comparison of acceptability in all age groups in period 1 and 2: Results of subjects receiving the oblong tablet in the first study period followed by syrup in the subsequent second study period order (solid line) and in the reverse treatment order (dashed lines). Application of treatment order "oblong tablet – syrup" in black, application of treatment order "syrup - oblong tablet" in red. O = oblong tablet, S = syrup.

Fig. 2B shows the acceptance rates for both treatments separately for period 1 and 2. The acceptance rate for the oblong tablet was a few percentage points higher in both periods compared to the acceptance rate of syrup. There appears to be no period effect, albeit the acceptance rate of both treatments is 3–5 %points lower in period 2.

On a descriptive basis the acceptability rate for the oblong tablet was consistently a few percentage points higher (75.0–100.0%) than that for syrup (71.4–92.9%) in all age groups and also in the group of male and female children. In general, the acceptability rates for both treatments improved with increasing age except for the age group 4 to < 5 years in which generally lower acceptability rates were observed than for the younger children.

The acceptability rates for male and female children were comparable and similar to the overall acceptability rates for oblong tablet and syrup.

4.3.2. Oblong tablet vs. mini-tablets (study arm B)

The overall acceptability rate of the oblong tablet (without consideration of periods) was 117 / 139 (84.2%) and the overall acceptability

rate of the mini-tablets was 121 / 139 (87.1%) (Fig. 3A). This resulted in a difference of −2.88% points with a 95% confidence interval (CI) of: (-7.31%, 1.55%). Thus, non-inferiority of the oblong tablet compared to the mini-tablets was demonstrated, while superiority of the oblong tablet to the mini-tablets could not be shown.

Fig. 3B shows the acceptability rates for both treatments separately for period 1 and 2. The acceptability rate for the oblong tablet was lower compared to the mini-tablets in period 1 while it was higher in period 2. However, the acceptability rates of oblong tablet and mini-tablets were comparable within both treatment sequences. The acceptability appeared to be higher in general (independent of the treatment) in the "mini-tablets – oblong tablet" sequence group compared to the "oblong tablet – mini-tablets" sequence group.

On a descriptive basis the acceptability rate for the oblong tablet was consistently a few percentage points lower than or equal (78.6–96.4%) to the acceptance rate for the mini-tablets (78.6–100.0%) in all age groups and also in the group of male and female children. In general, the acceptability rates for both treatments improved with increasing age from about 80% in the 1-year-old children to about 100% in the 5-year-old children.

The acceptability rates for male and female children were overall comparable and similar to the overall acceptability rates for oblong tablet and mini-tablets.

The difference in treatment sequence as described above for the overall analysis was also reflected in almost all subgroups.

4.4. Swallowability

The secondary outcome of swallowability was analyzed as binary outcome by analyzing only the first acceptability category ("*swallowed*" for the tablets or "*everything swallowed*" for syrup, respectively) as "swallowed" and all remaining acceptability categories as "not swallowed".

4.4.1. Oblong tablet vs. syrup (study arm A)

The overall swallowability rate of the oblong tablet (without consideration of periods) was 105 / 141 (74.5%), while the overall swallowability rate of syrup was much lower: 75 / 141 (53.2%) (Fig. 4A). This resulted in a difference of 21.26% points with a 95% confidence interval (CI) of (11.29%, 31.23%). Thus, not only non-inferiority of the oblong tablet compared to syrup was clearly shown,

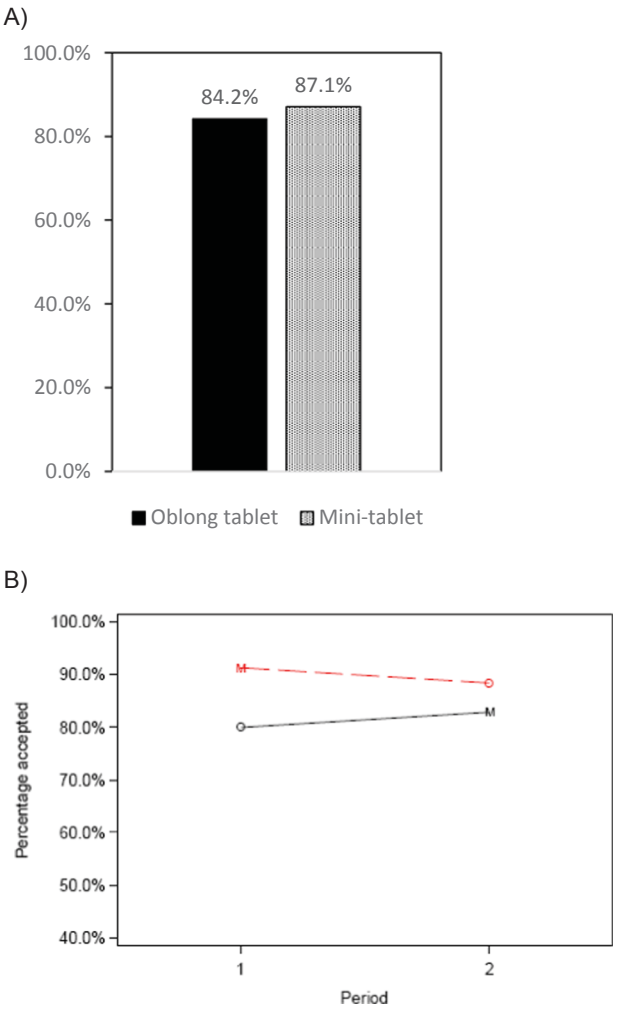

Fig. 3. Acceptability of oblong tablet in comparison to mini-tablets. (A) Overall age groups (B) Comparison of acceptability in all age groups in period 1 and 2: Results of subjects receiving the oblong tablet in the first study period followed by mini-tablets in the subsequent second study period order (solid line) and in the reverse treatment order (dashed lines). Application of treatment order "oblong tablet – mini-tablets" in black, application of treatment order "mini-tablets - oblong tablet" in red. O = oblong tablet, M = mini-tablets.

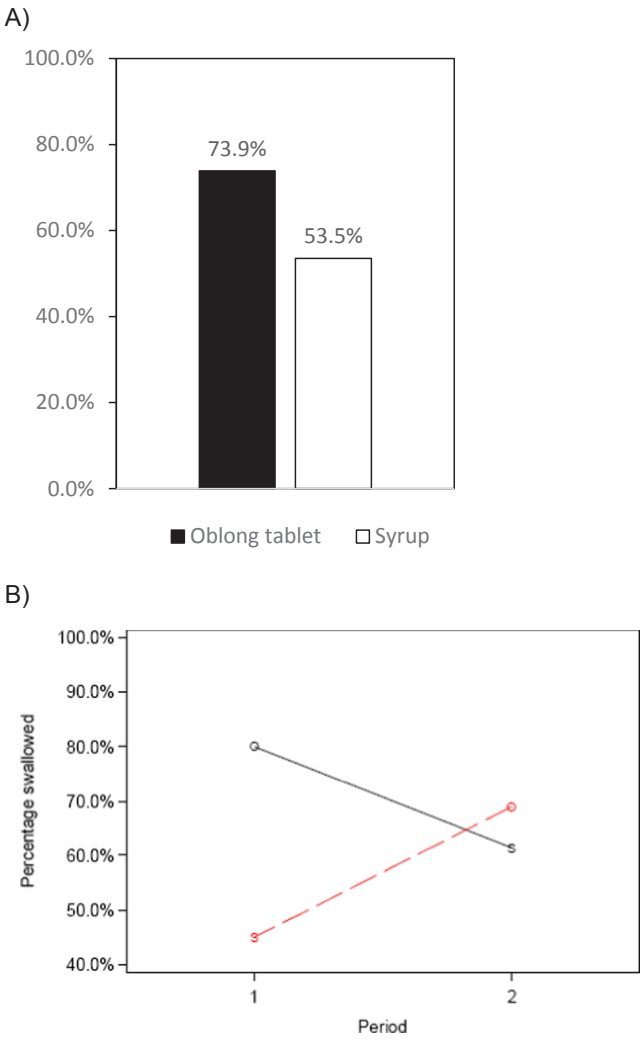

Fig. 4. Swallowability of oblong tablet in comparison to syrup. (A) Overall age groups (B) Comparison of swallowability in all age groups in period 1 and 2: Results of subjects receiving the oblong tablet in the first study period followed by syrup in the subsequent second study period order (solid line) and in the reverse treatment order (dashed lines). Application of treatment order "oblong tablet – syrup" in black, application of treatment order "syrup - oblong tablet" in red. O = oblong tablet, S = syrup.

but also superiority of the oblong tablet to syrup could be demonstrated with respect to swallowability. While the acceptability was comparable on a descriptive basis (84.4% for oblong tablet, 80.1% for syrup) the proportion of children who only partially swallowed the formulations was much higher after syrup (27.0%) than after the oblong tablet (9.9%).

Fig. 4B shows the swallowability rates for both treatments separately for period 1 and 2 for both sequence groups. The swallowability rate for the oblong tablet was considerably higher in the first study period (80.0%) compared to the swallowability rate of syrup (45.8%), whereas the difference between formulations was much smaller in the second period (68.1% vs 61.4%). No reason for this result could be identified. However, restricting the comparison of formulations to the first period in order to exclude any potentially confounding period or carry-over effects, superiority of the oblong tablet over syrup is evident.

On a descriptive basis, the swallowability rate for the oblong tablet was consistently higher (60.7–96.4%) than the swallowability rate for the syrup (39.3–64.3%) in all age groups. The difference raised from about 15 %points in the 1-year-old children to about 30 %points in 5-year-old children.

The swallowability rates in male and female children were comparable and similar to the overall result.

4.4.2. Oblong tablet vs. mini-tablet (study arm B)

The overall swallowability rate of the oblong tablet (without consideration of periods) was 108 / 139 (77.7%) and the overall acceptance rate of the mini-tablets was 111 / 139 (79.9%) (Fig. 5A).

This resulted in a difference of −2.12 %points with a 95% confidence interval (CI) of:

(-7.50%, 3.26%). Thus, non-inferiority of the Oblong tablet compared to the Mini-tablets was demonstrated with respect to swallowability, while superiority of the oblong tablet to the mini-tablets could not be shown.

Fig. 5B shows the swallowability rates for both treatments separately for period 1 and 2. The swallowability rate for the oblong tablet was overall comparable to that of the mini-tablets in both periods.

On a descriptive basis the swallowability rates for the oblong tablet (64.3–96.4%) and the mini-tablets (75.0–96.4%) were comparable within age and gender groups. In general, the swallowability rates increased with increasing age.

4.5. Palatability

Each evaluation of the palatability assessments (pleasant / no change / unpleasant) was performed by two different raters (rater 1 and rater 2).

4.5.1. Oblong tablet vs. syrup (study arm A)

The degree of agreement between the two raters was investigated by Cramér's V [20] measure of association. Cramér's V ranges between 0 (no agreement) and 1 (perfect agreement). The results were V = 0.599 for the palatability after the oblong tablet and V = 0.637 after syrup.

This is further illustrated in Fig. 6A and 6B below where more than two thirds of the palatability assessments were coinciding. The assessments matched in 99 / 141 (70.2%) subjects regarding the oblong tablet and in 106 / 141 (75.2%) subjects regarding syrup, including "not assessed".

Apart from one case, there were no completely contrary assessments where one rater assessed palatability as pleasant and the other as unpleasant. The assessments of both raters were evaluated separately.

Clearly, both raters assessed the reactions after the intake of the oblong tablet as unpleasant in only about 10% of the children while unpleasant reactions were detected in a much higher proportion of about 40% of the children after intake of syrup. Rater 1 identified a somewhat higher proportion of pleasant reactions after the oblong tablet and a considerably higher proportion of pleasant reactions after syrup compared to rater 2.

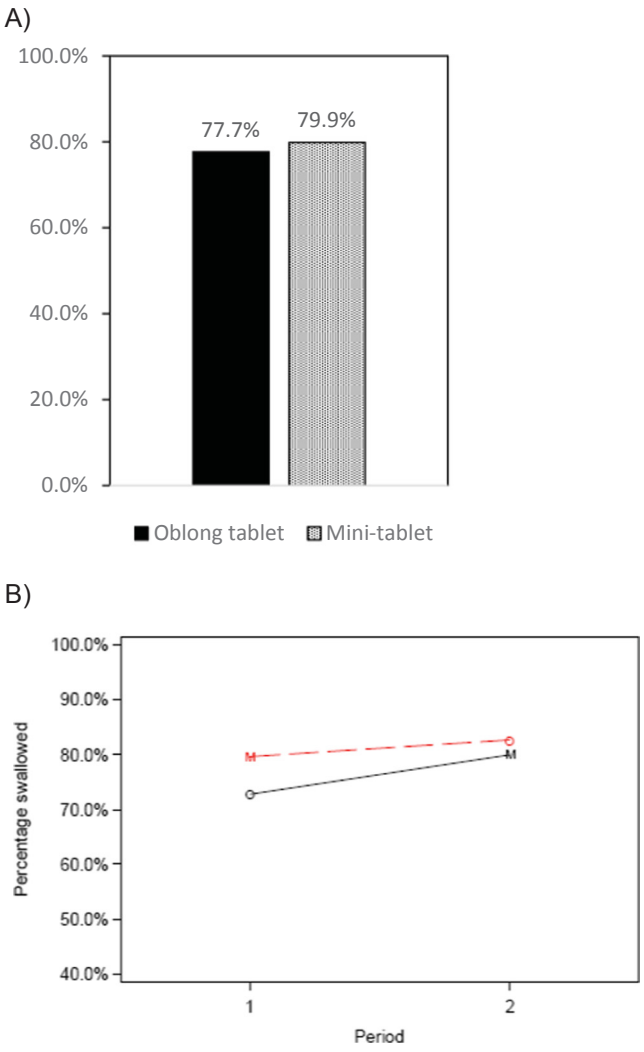

Fig. 5. Swallowability of oblong tablet in comparison to mini-tablets. (A) Overall age groups (B) Comparison of swallowability in all age groups in period 1 and 2: Results of subjects receiving the oblong tablet in the first study period followed by mini-tablets in the subsequent second study period order (solid line) and in the reverse treatment order (dashed lines). Application of treatment order "oblong tablet – mini-tablets" in black, application of treatment order "mini-tablets - oblong tablet" in red. O = oblong tablet, M = mini-tablets.

"Unpleasant" versus "no change or pleasant"

The comparison of the oblong tablet and syrup with regard to the proportion of "unpleasant"-judgements among all assessments resulted in the following estimated differences in palatability in the group of all children:

For rater 1: Difference in palatability "unpleasant": 27.71%, 95% CI: (18.00%, 37.42%)

For rater 2: Difference in palatability "unpleasant": 35.43%, 95% CI: (25.61%, 45.25%)

Thus, since both raters assessed syrup more frequently as unpleasant than the oblong tablet, superiority of the oblong tablet over syrup was clearly demonstrated. There appeared to be no period effects.

"Pleasant" versus "no change or unpleasant"

The comparison of the oblong tablet and syrup with regard to the proportion of "pleasant"-judgements related to all assessments resulted in the following estimated differences in palatability in the group of all children:

For rater 1: Difference in palatability "pleasant": 6.73%, 95% CI:

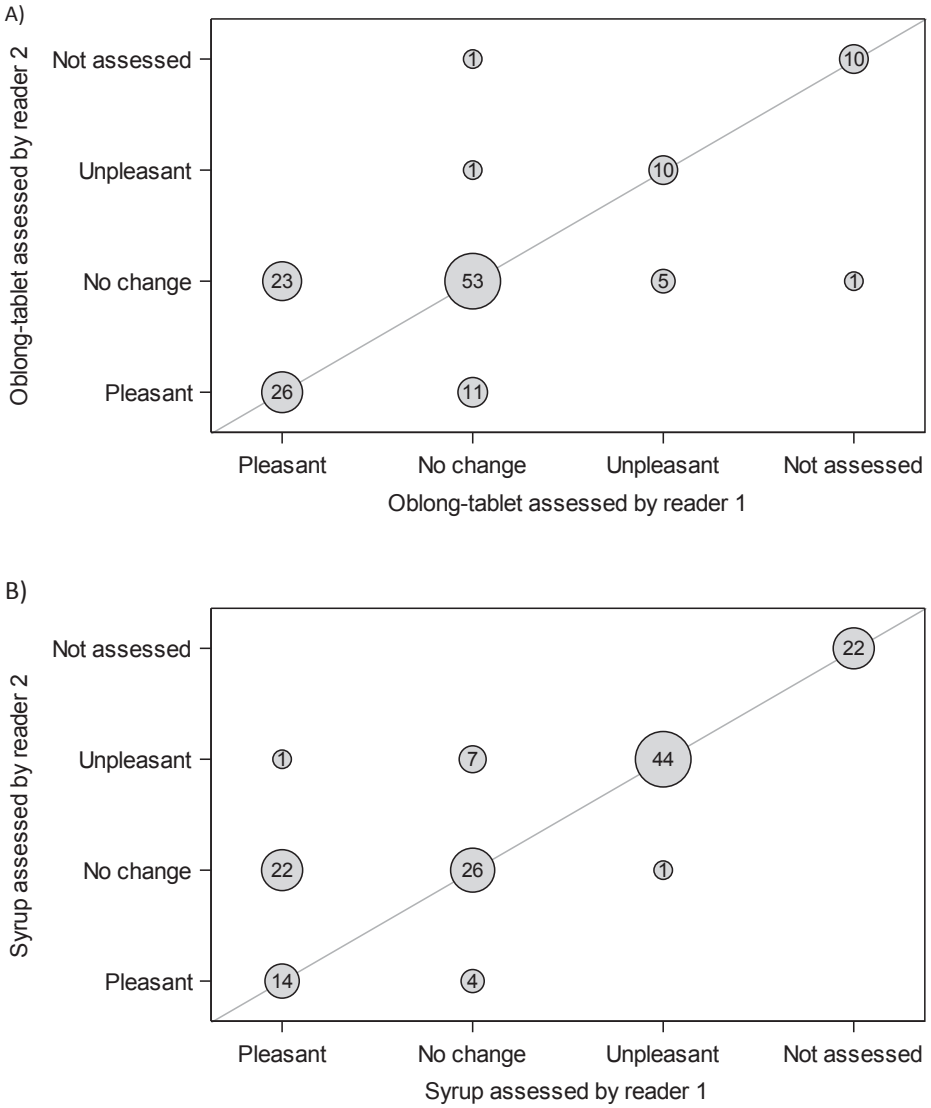

Fig. 6. Palatability of oblong tablet (A) and syrup (B) assessed by rater 1 and 2. The numbers of assessments in the respective categories are displayed inside the bubbles. Matching assessments between the two raters are located on the diagonal line.

(-1.67%, 15.14%)

For rater 2: Difference in palatability "pleasant": 15.53%, 95% CI: (6.04%, 25.01%)

Thus, the results of both raters clearly demonstrated non-inferiority of the oblong tablet compared to syrup with respect to the proportion of the palatability assessment "pleasant". Evidence for superiority of the oblong tablet was only indicated by the judgment of rater 2.

There appeared to be a discrepancy between both periods for rater 2 since the difference between oblong tablet and syrup was much more pronounced in the second period whereas the differences between oblong tablet and syrup appeared to be comparable in both periods for rater 1.

4.5.2. Oblong tablet vs. mini-tablets (study arm B)

The results of Cramér's V [20] as degree of agreement between the two raters were V = 0.546 for the palatability for the oblong tablet and V = 0.612 for the mini-tablets. This is illustrated in Fig. 7A and 7B below where approximately two thirds of the palatability assessments were coinciding. The assessments matched in 96 / 139 (69.1%) subjects regarding the oblong tablet and in 91 / 139 (65.5%) subjects regarding the mini-tablets, including "not assessed".

Apart from two cases, there were no completely contrary assessments where one rater assessed palatability as pleasant and the other as unpleasant. The assessments of both raters were evaluated separately.

Both raters rated the reactions as unpleasant in a small proportion of children after the oblong tablet as well as after the mini-tablets (about 6% unpleasant reaction after the oblong tablet and a comparable 7–8% after the mini-tablets. Rater 1 identified a somewhat higher proportion (about 10% points) of pleasant reactions after the oblong tablet as well as after the mini-tablets compared to rater 2.

"Unpleasant" versus "no change or pleasant"

The comparison of the oblong tablet and the mini-tablets with regard to the proportion of "unpleasant"-judgements related to all assessments resulted in the following estimated differences in palatability in the group of all children:

For rater 1: Difference in palatability "unpleasant": 0.81%, 95% CI: (-3.46%, 5.07%)

For rater 2: Difference in palatability "unpleasant": 0.82%, 95% CI: (-4.05%, 5.69%)

Thus, the palatability assessments were comparable between oblong tablet and mini-tablets for both raters. The oblong tablet was non-inferior to the mini-tablets. There appeared to be no period effects.

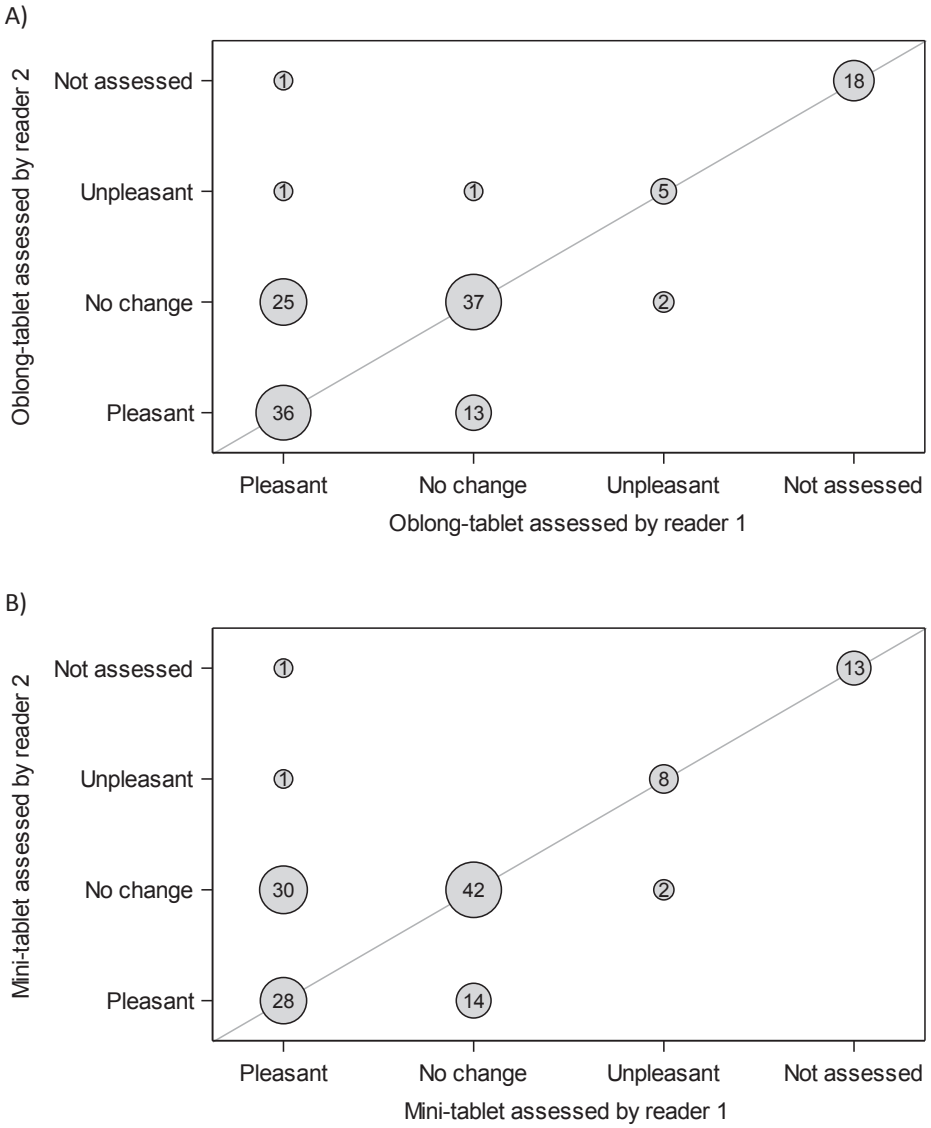

Fig. 7. Palatability of oblong tablet (A) and mini-tablets (B) assessed by rater 1 and 2. The numbers of assessments in the respective categories are displayed inside the bubbles. Matching assessments between the two raters are located on the diagonal line.

"Pleasant" versus "no change or unpleasant"

The comparison of the oblong tablet and the mini-tablets with regard to the proportion of "pleasant"-judgements related to all assessments resulted in the following estimated differences in palatability in the group of all children:

For rater 1: Difference in palatability "pleasant": 2.31%, 95% CI: (-2.38%, 7.00%)

For rater 2: Difference in palatability "pleasant": 5.70%, 95% CI: (-0.82%, 12.21%)

Again, the results of both raters clearly demonstrated non-inferiority of the oblong tablet compared to the mini-tablet with respect to palatability. There was no evidence for superiority.

5. Discussion

The primary objective of this study with non-inferiority regarding acceptability of the oblong tablet compared to syrup (study arm A) was demonstrated in the group of all children aged 1 to under 6 years. With respect to swallowability not only non-inferiority but also superiority of the oblong tablet compared to syrup could be shown. Palatability of the oblong tablet was superior to syrup considering the proportion of "unpleasant" assessments for two independent raters. When considering the proportion of "pleasant" palatability assessments, superiority of the oblong tablet was demonstrated for one rater, while for the second rater the difference between the two formulations was also in favor of the oblong tablet but less pronounced.

The results with respect to acceptability, swallowability and palatability of the oblong tablet and the mini-tablets (study arm B) were highly comparable. Thus, non-inferiority of the oblong tablet compared to the mini-tablets was demonstrated for all three endpoints. As the same pharmaceutical excipients have been chosen for both tablets non-inferiority can trace back to tablet geometry.

Since the required sample size of 132 evaluable cases per study arm was exceeded (arm A: N = 141, arm B: 139), high power of this study was assured, and thus high credibility and validity of the study results can be assumed. Furthermore, since about 140 children were valid for analysis in each study arm (as anticipated), all age groups were appropriately and nearly equally sized.

For the first time the suitability of small oblong tablets in children could be demonstrated. However, our findings are in line with previous studies by our group and others regarding the general acceptability of mini-tablets in children aged between 6 months and 6 years by

demonstrating their ability to swallow multiple solid dosage forms (up to 400 mini-tablets) simultaneously.

Oblong tablets are larger solid dosage forms than mini-tablets but the results of this trial have demonstrated that infants and toddlers are able to accept and swallow even those larger tablets without a risk. We conclude that oblong tablets, which can be used to achieve a higher active ingredient load per administration, were also a suitable alternative to the standard syrup and an alternative to three simultaneously administered mini-tablets. This assumption was supported by the fact that the acceptance rates and swallowability rates of oblong tablets in each age group exceeded those of syrup.

Regarding palatability, the oblong tablet was also preferable to syrup. This could be relevant if a drug needs to be given several times or over a longer period of continuous use. No adverse event occurred during the study, so that among our data no risk from oblong tablets can be suspected.

A limitation of the study was the lack of long-term administration. Furthermore, the opinion of the participating patients or parents concerning their perception and formulation preference was not object of this study. The oblong tablets are a suitable way of providing medical care to children in poorly supplied areas of the world due to their easy storage and long stability. As manufacturing costs can be significantly reduced by large manufacturing batches, the oblong tablets could be a cost-conscious, easy to transport pediatric formulation. Another limitation of the present study is that we only investigated drug-free formulations. Adding an active pharmaceutical ingredient, e. g. with poor taste sensations or unpleasant texture (mouthfeel), could require different measures, e.g. addition of sweeteners, flavours, or coatings. These may impact the overall acceptability of the final formulation.

The oblong tablets thus provide a useful alternative to the mini-tablet, especially when higher doses of active substance are required. Based on our systematic research, clinical researchers can now use these validated evaluation criteria to evaluate the suitability of active substances in oblong tablets for the long-term treatment of patients. Our data close the gap in the current data supporting solid oral drug formulations and open the perspective for the introduction of such oblong tablets for children of all ages, thus continuing the paradigm shift from liquid to solid drug formulations for children as proposed by the WHO.

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Data sharing statement

Individual participant data will be available (including data dictionaries). Particularly individual participant data that underline the results reported in this article will be shared after deidentification. The data will be available beginning 3 months and ending 5 years following the article publication. The data will be available for researchers who provide a methodologically sound proposal to achieve aims in the approved proposal. The proposal should be directed to Viviane. klingmann@med.uni-duesseldorf.de. To gain access, data requestors will need to sign a data access agreement.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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3 Discussion

With this study, we are the first to examine acceptability, swallowability, and palatability of small oblong tablets in childhood. Herein we contribute to the development of new oral dosage forms in children, consequently assisting the paradigm shift from liquid to solid drug formulations for children, as intended by the WHO.

3.1 Acceptability

78.6% of 1-2-year-olds accepted oblong tablets and 75% accepted syrup, whereas 100% of 5-6-year-olds accepted oblong tablets and 92.9% accepted syrup. Acceptability for oblong tablets, as well as syrup, thus increased with the age of the children.

An exception are the 4-5-year-olds (total acceptability oblong: 75%, total acceptability syrup: 71.4%), who showed a lower acceptability rate than the 3-4-year-olds (total acceptability oblong: 89.7%, total acceptability syrup: 86.2%). This could be due to picky eating in preschool children [133].

An increase in acceptability in older children was also observed in comparison of mini-tablets to oblong tablets (1-2-year-olds: total acceptability oblong: 78.6%, total acceptability mini-tablet: 78.6%, 5-6-year-olds: total acceptability oblong: 96.4%, total acceptability mini-tablet: 100%).

This implies, that each dosage form is better accepted as children get older. Studies investigating the administration of multiple formulations should be screened for a periodic effect.

The acceptability of oblong tablets was higher in the group, that received first mini-tablets and then oblong tablets, than in the group, that received initially oblong tablets and subsequently mini-tablets. One reason for this could be the increase in the size of the solid dosage form from small (mini-tablet, 2 mm x 2 mm) to larger (oblong tablet 2,5 mm x 6 mm) and therefore habituation.

For the acceptability in study arm A (oblong vs. syrup) there appears to be no periodic effect, albeit the acceptance rate of both treatments is 3-5% points lower in period 2. This is particularly impressive in the group of 1- to 2-year-olds. While 92.9% of the oblong tablets administered in period 1 were accepted, only 64.3% of those administered in period 2 were accepted. This could be due to an aversion to syrup and, as a result, a refusal to take further formulations, especially in this age group.

The acceptability rates for male and female children were comparable and similar to the general acceptability rates, which met our expectations.

A dosage form was also considered accepted, if children chewed it. Of course, this could have an influence on the bioavailability and the absorption of the active substance into the organism. In addition, an unpleasant taste may arise, when chewing a tablet with active ingredient, so that the acceptability would be reduced as a consequence. However, our study was focused on the acceptability of active ingredient-free tablets. These concerns would have to be considered in follow-up studies involving active ingredients.

3.2 Swallowability

The swallowability of oblong tablets was significantly higher (74.5% over all age groups) than that of syrup (53.2% over all age groups), especially in the group that initially received the oblong tablet. This is due to the fact, that the syrup was frequently not taken in the full dose (27.0% syrup vs. 9.9% oblong tablet).

This is remarkable, as the syrup had a sweet taste, while the oblong tablet and the mini-tablets were tasteless. The tasteless dosage form (oblong tablet) was thus swallowed more frequently in the full dose than the sweet dosage form (syrup). Hence, one can conclude, that not the taste, but the type of formulation (solid formulation, geometry) was decisive for whether a formulation was swallowed completely or not.

For mini-tablets and oblong tablets comparable swallowability rates were found.

It was noticeable, that especially for the young children (age groups 1 and 2) the swallowability of oblong tablets when compared to mini-tablets was significantly lower when they were given first than when they were given second (age group 1: 50% (period 1) vs. 78.6% (period 2), age group 2: 66.7% (period 1) vs. 85.7% (period 2)). This phenomenon was leveled off with increasing age. Interestingly, the swallowability of the oblong tablets, when compared to syrup, was significantly higher in age group 1 when the oblong tablet was given first (85.7% (period 1) vs. 50% (period 2)). A slight tendency in this direction was also seen across all age groups (oblong tablets vs. syrup: 80% period 1, 69% period 2, oblong tablets vs. mini-tablets: 72.9% period 1, 82.6% period 2).

This periodic effect could be due to the fact, that after the syrup, the children did not want to tolerate any further intake. In the contrary, after taking the mini-tablets, on the other hand, it was easier to take a slightly larger tablet, presumably as they got accustomed to it.

As expected, swallowability also increased with age and no gender differences were observed.

It must be taken into account, that in case of bitter APIs, a lower swallowability might result with syrup, mini-tablets and oblong tablets containing active substances. In syrup the bitter taste of an active ingredient is often masked by different flavors [134-137]. For mini-tablets and oblong tablets, coating would be a way to mask bitter taste.

In addition to that, the taste preferences of the individual must be taken into consideration.

3.3 Palatability

Regarding palatability, there was also no significant difference found between mini-tablets and oblong tablets. However, the syrup was more often (40%) evaluated with an "*unpleasant*" reaction than the oblong tablets (10%). This could be a reason for the lower swallowability of the syrup compared to oblong tablets.

The parameters acceptability and swallowability used in this study were already established in previous studies of the working group and applied to about 900 participants [125-129]. Palatability, meanwhile, was added for the second time, after the study groups clinical trial on the suitability of ODFs [129]. According to EMA, children under the age of 5-6 years are not able to communicate their taste preferences [107]. It was of importance to our study group to obtain an objective assessment of palatability. Therefore, it had been decided to have two independent physicians assess palatability via video. This was conducted on the basis of the children's facial expressions and verbal comments, as well as motions (e.g., defensive movements of the arms and head). The advantage therein was, that the study team member performing the test could concentrate on the assessment of acceptability and swallowability. Except in three cases, there were no completely contrary assessments, in which one reader assessed palatability as pleasant and the other one as unpleasant. This underlines the reliability of this method. Thus, we have established a method, how, contrary to the assumption of the EMA, it is possible to distinguish between good and bad taste of an administered formulation even in young children.

In further studies, a facial hedonic scale could also be used for the assessment in older children, as recommended by the EMA. It must be remembered, however, that facial expression can be influenced not only by palatability, but also by acceptability.

Furthermore, parents or guardians could be questioned about the child's reaction (e.g. with questionnaires) [107].

3.4 Safety

During the conduct of this study, no adverse events occurred while taking any of the formulations. This indicates that oblong tablets are a safe alternative to gold standard syrup and mini-tablets, which have already been tested by the study group on 889 patients. Nevertheless, the number of participants in our study is not sufficient to fully confirm the safety of the oblong tablet.

However, oblong tablets in this size are an absolute novelty. Accordingly, so far there are no previous studies on this type of dosage form.

3.5 Recruitment

In total, the guardians of 358 children were approached. 79% agreed to participate. This very high recruitment rate could be due to the fact, that parents are familiar with the problem of administering syrup and therefore have a great interest in participating in the development of new oral dosage forms. Furthermore, study participation took a modest amount of time and could be done while waiting for an appointment. In addition, many parents were willing to participate, because it was only a one-time administration of a placebo formulation. The fact, that the study was conducted by physicians and a PhD student at the clinic, could have contributed to the parents' trust. Moreover, parents could let their children participate confidently, as there was no great risk for the children.

The highest refusal rate was found in age group 2, where 21 guardians declined to participate. The lowest refusal rate was in age group 3, where only 8 guardians rejected participation. The main reason for non-participation was the unavailability of the second parent (see 1.3.3). The second most common reason was refusal by the mother or father because of a lack of interest in participating in a clinical trial. A language barrier was also a frequent reason for non-participation.

Accordingly, the participation rate could still be increased, if the contactability of the absent parent could be improved. In our study, we informed the absent parent by telephone and had a witness sign on behalf of this parent.

3.6 Previous studies

As this is the first study investigating acceptability, swallowability and palatability of small oblong tablets in children, we cannot compare the results to those of any other working groups. At this point, however, the studies conducted on mini-tablets deserve to be discussed.

The intake of mini-tablets has already been investigated in numerous studies.

Thomson et al. found an ascending acceptability with increasing age in their study with 100 children between 2 and 6 years of age and mini-tablets of 3 mm in diameter an ascending acceptability with increasing age. "*The proportion increased to 53% for children 3 years of age. Children ≥4 years of age were more likely to swallow the mini-tablet than not to swallow the mini-tablet, with 85% of 5-year-old children swallowing the mini-tablet*" [119].

Smaller mini-tablets with a diameter of 2 mm, which were tested by our working group, showed no significant correlation of acceptability with the age of the children [126]. Accordingly Kluk et al. [122] concluded after their study with different numbers (5-10) and sizes (2 mm or 3 mm) of mini-tablets, that "*neither the number nor the diameter of the administered mini-tablets have significantly influenced the ability to swallow units*"[122]. In the study performed by our working group on the acceptability of multiple mini-tablets between the ages of 6 months and 5 years, we found that even up to 400 mini-tablets are acceptable for children [128]. Van Riet-Nales et al. [120] compared four oral dosage forms without active ingredient in 143 children between 1 and 4 years of age in terms of acceptability, which was evaluated by the parents, who filled out a questionnaire after administration. They did not divide the children in their study into age groups but evaluated them collectively. This precludes any statement as to whether a correlation between age and acceptability can be deduced for the 4 mm diameter mini-tablets they used [120].

In 2020, Bracken et al. found an inverse correlation of tablet size and acceptability in children aged 4-12 years, testing bigger placebo tablets of 6 mm, 8 mm and 10 mm diameter. The authors explain this phenomenon with a potential learning effect, as they were administered smallest to largest [124]. These results indicate that children can also swallow tablets with ≥ 6 mm size. They were able to identify an age correlation in the swallowability of the tablets. However, this is not statistically reliable due to the small number of participants (55 participants in total).

It therefore remains uncertain, whether the acceptability of mini-tablets of a certain size correlates with the age of the children. However, both studies, in which multiple mini-tablets were administered, showed no correlation between the number of mini-tablets and swallowability [122, 128].
In our recent study, we found a link between age and the rate of acceptability of oblong tablets.
No adverse events occurred in any of the mentioned studies. Thus, after Thomson et al.'s study, it could be concluded, that larger tablets can be taken from the age of 4 years [119]. This age could be corrected down to >1 year by the study of Van Riet-Nales, in which children swallowed mini-tablets with a diameter of 4 mm [120]. Kluk et al. then showed, that children between 2 and 3 years of age can also swallow multiple mini-tablets with a diameter of 2 or 3 mm. Smaller mini-tablets of 2 mm diameter were tested by Van de Vijver et al. on 16 children aged 6 months and older [121]. Due to the small number of participants, however, the significance of this study is limited. A study conducted in our hospital with a collective of 306 patients confirmed the safety of the mini-tablets of 2 mm diameter in this age group [126]. Additionally, our study team was able to demonstrate a non-inferiority of mini-tablets of 2 mm diameter compared to syrup in 151 newborns [127].

Thus, mini-tablets were found to be a safe alternative to the gold standard syrup in various studies and in testing on about 1500 children.

In our study we chose the lower age limit for the intake of oblong tablets to be one year of age.

The new dosage form of the oblong tablets now offers the possibility to administer five times as much active ingredient per tablet as in a mini-tablet of 2 mm diameter. This can be particularly advantageous, when there is a high requirement for active ingredients. In addition, its shape and size make it easier to handle than the very small mini-tablets.

In the studies of other working groups described above, there were some differences to the design of the studies conducted by Klingmann et al.
In Thomson et al.'s trial, a second attempt to swallow, which was successful after the child had taken the tablet out of its mouth, was considered as "*swallowed*", whereas we considered it "*refused to take*"[119]. This information must always be kept in mind when assessing the data, as correspondingly different swallowability rates are to be expected.

In contrast to our study, no comparison was made to the gold standard syrup. Accordingly, no non-inferiority or even superiority could be demonstrated.

In Van Riet-Nales et al.'s trial, the administration of the dosage forms took place at home in the usual family routine on four consecutive days. Accordingly, the study depicts a realistic picture of medication administration in a longer-term family setting. In our studies, on the other hand, the formulation was always administered once by a healthcare professional, so that neither the administration of the formulation in a familiar environment, nor over a longer period of time can be assessed.

In Van Riet-Nales et al.'s study, the children were included in the evaluation via a VAS-score and the parents filled out a questionnaire. This inclusion of patient opinion was not implemented in our studies. However, an assessment by patients and their parents is very relevant, as they are the ones, who might use the new formulations in the future. As no evaluation by an independent expert took place in Van Riet-Nales et al.'s trial, the objectivity of the results cannot be guaranteed. Whether the formulation was chewed was not evaluated, in contrast to our study. However, this information is of great importance, as chewing tablets could release the bitter substances of the API and thus reduce swallowability.

3.7 Limitations

A limitation of the study is that no repetitive administrations were assed, so any conclusions we draw are based on a single dose. Furthermore, the formulation was administered in an unfamiliar environment and by a foreign person. As a result, it is not possible to assess how the results would change if the formulation was administered by the parents in their domestic environment. In addition, children from outpatient and inpatient sectors of our university hospital were included. No information was collected on the underlying diseases of the children. In this respect, it cannot be estimated, how many chronically ill children who may already be used to medication were included. In order to reduce the number of these already "*trained*" children, recruitment was not undertaken in the oncology outpatient clinic or on the children's oncology ward. Of note, dosage forms free of active ingredients were used. Consequently, no statement can be made about the potential mode of action of the active pharmaceutical ingredient after administration in oblong tablets. Moreover, we did not consult patients, their parents or

guardians about their perception, even if those would have to cope with the formulation. Our study was conducted in an open, non-blinded scheme, which poses a higher risk for investigator and patient bias.

3.8 Prospects

The uniqueness of this study is that no reliable data on the acceptability, swallowability and palatability of oblong tablets in childhood has been published yet.

Further studies are needed to establish oblong tablets as an alternative dosage form. The acceptability of oblong tablets should be evaluated over a longer period of time. The simultaneous intake of several oblong tablets could be evaluated, as this might become relevant with higher doses. In addition, *coated* oblong tablets should also be tested for acceptability, palatability and swallowability to make taste masking in oblong tablets possible. Furthermore, the comparison of syrup and oblong tablets should be made with integrated active ingredient. The high manufacturing costs would be significantly reduced by large production batches and thus the oblong tablets could be a cost-saving, easy to transport formulation. Therefore, it could be a way of providing medical care to children in poorly supplied areas of the world, due to its easy storage and long shelf life [107].

4 Conclusion

This trial compared acceptability, swallowability and palatability of 3 oral dosage forms in 283 children aged 1 to 5 years inclusively. It compares the gold standard syrup, as well as the newly established mini-tablets, against a new oral dosage form using established and relatively new innovative criteria and methods. In this direct comparison, it could be shown that the new oblong tablet is not inferior to or even superior to the syrup in the parameters applied. This leads to the conclusion, that oblong tablets are a suitable alternative to the former gold standard syrup and the already extensively tested mini-tablets, especially when large amounts of active ingredient are required. The significant and reliable data collected in this study represent a further step in the development of child-appropriate dosage forms. It must be the aim to reduce the massive off-label and off-licensed use of drugs in pediatrics and to guarantee the safety of drug administration by means of adequate dosage forms.

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6 Attachement

6.1 Study protocol

Protocol

A Randomized, Single Dose, Two Parallel Groups, Cross-over Study to Investigate the Acceptability, Swallowability, and Palatability of Three Oral Placebo Formulations in Young Children

Protocol Number: 2018 – 001 (Vs.1.0)

Deutsches Register Klinischer Studien:
Register Number DRKS00014341

Study Register of the Medical Faculty of the Heinrich-Heine-University:
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Investigator Initiated Trial

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Düsseldorf, 22.03.2018

Confidential

Summary Information

Title:	A Randomized, Single Dose, Two Parallel Groups, Cross-over Study to Investigate the Acceptability, Swallowability, and Palatability of Three Oral Placebo Formulations in Toddlers
Protocol Number:	2018-001 (Vs. 1.0)
Principal Investigator and Protocol Author:	Dr. med. Viviane Klingmann Klinik für Allgemeine Pädiatrie, Neonatologie und Kinderkardiologie Universitätsklinik Düsseldorf Moorenstraße 5 40225 Düsseldorf
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In Collaboration with:	Prof. Dr. Jörg Breitkreutz Institut für Pharmazeutische Technologie und Biopharmazie Heinrich-Heine-Universität Düsseldorf Universitätsstraße 1 40225 Düsseldorf
Statistician:	Dr. Frauke Friedrichs M.A.R.C.O. GmbH & Co. KG Schirmerstr. 71 40211 Düsseldorf

Placebo Formulations

Manufacturers: Oblong-tablet 2,5 x 6 mm uncoated
Manufacturer: NextPharma PHARBIL Waltrop GmbH
Im Wirrigen 25
45731 Waltrop

Mini-tablet ø 2mm uncoated
Manufacturer: NextPharma PHARBIL Waltrop GmbH
Im Wirrigen 25
45731 Waltrop

Glucose-Syrup
Manufacturer: Caesar & Loretz GmbH
Herderstraße 31
40721 Hilden

Signatures:

…….	……..
Dr. Viviane Klingmann Principal Investigator, Protocol Author	Date
…….	……
Dr. Hans Martin Bosse Co-Investigator	Date
…….	……
Prof. Dr. Jörg Breitkreutz Co-Investigator	Date
…….	……
Dr. Frauke Friedrichs Statistician	Date

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Table of Contents Page

Glossary

AE	Adverse Event
AMG	Arzneimittelgesetz
AR	Adverse Reaction
CDMS	Clinical Data Management System
CRF	Case Report Form
ø	Diameter
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
°C	Grad Celsius
HIV	Human Immunodeficiency Virus
IEC	Independent Ethics Committee
KKS	Koordinationszentrum für Klinische Studien
mm	Millimetre (s)
ml	Millilitre (s)
N	Number
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction

1 Synopsis

1.1 Title

A Randomized, Single Dose, Two Parallel Groups, Cross-over Study to Investigate the Acceptability, Swallowability, and Palatability of Three Oral Placebo Formulations in Toddlers

1.2 Objectives

1.2.1 Primary Objectives

To demonstrate non-inferiority in acceptability of the oblong-tablet in comparison to 3 ml glucose syrup in children aged between 1 year and 5 years inclusive.

1.2.2 Secondary Objectives

To demonstrate non-inferiority in acceptability of the oblong-tablet in comparison to three mini-tablets in children aged between 1 year and 5 years inclusive.

To compare swallowability of the oblong-tablet and of 3 ml glucose syrup in children aged between 1 year and 5 years inclusive.

To compare swallowability of the oblong-tablet and of three mini-tablets in children aged between 1 year and 5 years inclusive.

To compare acceptability of an oblong-tablet and of 3 ml glucose syrup in subsets of children aged 1 to 2 years, 2 to 3 years, 3 to 4 years, 4 to 5 years and 5 to 6 years.

To compare acceptability of an oblong-tablet and of three mini-tablets in subsets of children aged 1 to 2 years, 2 to 3 years, 3 to 4 years, 4 to 5 years and 5 to 6 years.

To compare swallowability of an oblong-tablet and of 3 ml glucose syrup in subsets of children aged 1 to 2 years, 2 to 3 years, 3 to 4 years,4 to 5 years and 5 to 6 years.

To compare swallowability of an oblong-tablet and of three mini-tablets in subsets of children aged 1 to 2 years, 2 to 3 years, 3 to 4 years, 4 to 5 years and 5 to 6 years.

To compare the palatability of an oblong-tablet, three mini-tablets and 3 ml syrup in each age group.

To identify any possible problem that could occur during deglutition.

To identify the percentage of children who inhaled or coughed during ingestion of any of the oral placebo formulations.

To investigate the safety of the oral placebo formulations.

To investigate the percentage of approached parents consenting to participation of their child in this study.

To identify reasons why approached parents are not willing to agree to the participation of their child in this study.

1.3 Design and Randomisation

This study will be performed in two parallel groups (study arms) in a single-centre, open, randomised, single dose, two-way cross-over design with age-stratification into five groups. The children are stratified into the following five age groups: 1 to <2 years, 2 to <3 years, 3 to <4 years, 4 to <5 years and 5 to <6 years. Each age group has two study arms.

Randomisation within each age group will be performed as follows:

At first, when the child has been assessed as eligible for the trial, it will be randomized to one of the two study arms A or B:

A: Children will receive one oblong-tablet and 3 ml glucose syrup in the order assigned by randomisation.

B: Children will receive one oblong-tablet and three 2 mm mini-tablets in the order assigned by randomisation.

1.4 Population

The parents of approximately 600 children, aged between 1 and 5 years inclusive, will be approached and informed consent to study participation sought. Those children who satisfy all in-/exclusion criteria according to the judgement of the investigator at the paediatric hospital will be scheduled for enrolment. Up to 300 paediatric patients will be enrolled to achieve 280 evaluable paediatric patients in two parallel groups (140 children per parallel group) and 28 evaluable patients in each sub-group that meet the in-/exclusion criteria. They will be randomised to the order of application of the respective two oral placebo formulations.

1.5 Formulations under Examination

1 Oblong-tablet 2,5 x 6 mm uncoated (without active ingredient)
3 Mini-tablets ø 2mm uncoated (without active ingredient)
3 ml Glucose-Syrup 15% (without active ingredient)

1.6 Examination Plan

After provision of detailed oral and written information to the parents about the study, its relevance, benefits and risks the signed Informed Consent will be obtained from the parents and Assent will be obtained from the children after age-adapted information. The in- and exclusion criteria will be assessed and those children suitable for enrolment into the study will be randomised to the parallel group and the sequence of placebo formulations in this age sub-group according to the randomisation scheme. After an oral inspection using a tongue depressor and a torch the children will receive either the oblong-tablet with a drink of choice or three mini-tablets with a drink of choice or 3 ml of the glucose syrup administered with an oral syringe with a drink of choice. The process of deglutition and physical reactions will be observed and the result of swallowing assessed by oral inspection. As soon as the child is ready for the second part of the examination, the administration and assessment procedure will be repeated with the other formulation.

The following evaluation criteria will be assessed:

Acceptability and Swallowability:

Oblong-tablet and mini-tablets:

- Swallowed
  - which implies that no chewing took place during deglutition and no residuals of the solid were found during oral inspection
  - interpreted as accepted and swallowed
- Chewed
  - which implies that chewing was observed before deglutition or that the whole or parts of the solid were found during oral inspection
  - interpreted as accepted but not swallowed
- Spat out
  - which means that no deglutition took place and that the solid is no longer in the child's mouth
  - interpreted as not accepted and not swallowed
- Choked on
  - which means that the solid was swallowed the wrong way or that a cough was caused
  - interpreted as not accepted and not swallowed
- Refused to take
  - which implies that the child didn't allow the investigator to place the solid in the mouth
  - interpreted as not accepted and not swallowed

Glucose syrup:

- Everything swallowed

    - which means that no liquid was left in the mouth and no drops left the mouth
    - interpreted as accepted and swallowed
- Small runlet flowing out of the mouth or leftover in the syringe
    - which means that the child did not swallow completely
    - interpreted as accepted but not swallowed
- Spat out
    - which means that no deglutition took place because the child disgorged the glucose syrup directly
    - interpreted as not accepted and not swallowed
- Choke on
    - which means that the syrup was swallowed the wrong way or that a cough was caused
    - interpreted as not accepted and not swallowed
- Refused to take
    - which implies that the child didn't allow the investigator to place the syringe in the mouth or that the child didn't close the mouth correctly and that all glucose syrup was leaking out of the mouth because no deglutition took place
    - interpreted as not accepted and not swallowed

Palatability:

	Criterion	Interpretation	Description of Reaction
①	Pleasant	Positive hedonic pattern	Tongue protrusion, smack of mouth and lips, finger sucking, corner elevation
②	No change	Neutral	Neutral mouth movements (irregular and involving lips)
③	Unpleasant	Negative aversive pattern	Gape, nose wrinkle, eye squinch, frown, grimace, head shake, arm flail

Palatability will be documented by videotaping for central evaluation by two blinded independent experienced and trained readers.

1.7 Study Duration and Timings

The study duration per child will comprise maximum 2 days of activity: when parents and children are interested in participating in the study and the child seems to fulfil the inclusion and exclusion criteria according to the investigator, parents and child will be invited to a participant information and Informed Consent/Assent session. After having signed the Informed Consent Form/provided Assent, the in- and

exclusion criteria will be assessed and suitable children will be enrolled and randomised to the group and sequence of formulation administration. The two formulations will be applied within 15 minutes. After complete assessment and verification of the child's wellbeing, the child will be released from the study.

1.8 Statistical Evaluation

Statistical methods:

The statistical analysis will be performed separately for each study arm (oblong-tablet in comparison to syrup and oblong-tablet in comparison to mini-tablets) of this trial.

Demographic data and baseline characteristics will be summarised descriptively by sequence group and overall. Efficacy and safety data will be summarised descriptively by treatment. Descriptive statistics will also be presented broken down by age groups. Categorical data will be summarised by frequencies and percentages, continuous data by number of observations, means, standard deviation, minimum, first quartile, median, third quartile and maximum.

The primary outcome of acceptability will be analysed as binary outcome by combining the first two acceptability categories (swallowed / chewed for the tablets or everything swallowed / small runlet for syrup, respectively) as "accepted" and the three remaining acceptability categories as "not accepted".

The acceptability will be compared between both treatments by applying the analysis proposed by Schouten and Kester. At first, the difference in acceptability rates of the oblong tablet versus the reference product will be estimated for each sequence group and then averaged over both sequence groups in a second step. Corresponding one-sided 97.5% confidence intervals will be calculated for the averaged difference of acceptability rates.
The oblong-tablet will be considered as non-inferior in comparison to the reference product, if the lower limit of the one-sided 97.5% confidence interval for the averaged difference in acceptability rates (pOblong-tablet - pReference) exceeds -15%-pts.
The corresponding hypotheses to be tested are:
H0: πOblong-tablet ≤ πReference – 15% versus H1: πOblong-tablet > πReference – 15%, where π denoted the true probability for acceptance.
If non-inferiority of the oblong tablet to reference could be concluded, then superiority could be tested subsequently. Superiority could be concluded if the one-sided 97.5% confidence interval for the difference in acceptability rates (pOblong-tablet - pReference) does not include zero.

Frequencies of acceptability ("accepted" / "not accepted") will be tabulated by treatment. Moreover, 2x2 contingency tables will be provided presenting paired samples (i. e. result after Oblong-tablet versus result after reference).

Similar analyses as described above will also be performed for each of the five age groups in exploratory manner.

The secondary outcomes of swallowability and palatability will also be analysed as binary outcome and the analyses will be performed analogously to the analysis of acceptability.

Sample size calculation:
The sample size required to meet the primary objective is based on an acceptance rate of the syrup of 80% as observed in our previous clinical studies. Furthermore, the following assumptions are made:
Non-inferiority margin: 15%-pts
Significance level: $\alpha = 2.5\%$ (one-sided)
Power: 90%
Correlation: r=0.3
Sample size calculation results to a total number of 132 evaluable cases.
Since this design is stratified by 5 age groups, and each age group has to be balanced by treatment sequence, 140 children are required for the study arm with syrup as reference (i.e. 28 children per age group).

With regard to the secondary objective (to demonstrate non-inferiority in acceptability of the oblong-tablet in comparison to three mini-tablets), the acceptance rate of the mini-tablet is expected to be higher than 80% (up to 90%). Thus, less children would be needed. However, a sample size of 140 children will be chosen as in the other study arm to get a more precise estimate of the acceptability rates in the age groups.

Thus, both study arms need to include 280 children in total.

1.9 Reporting

This study has been registered in “Deutsches Register Klinischer Studien” and in the „Study Register of the Medical Faculty of the Heinrich-Heine-University”. It will be subject of a doctoral thesis and the results will be reported in form of a publication in a well-established journal and in form of a poster or a presentation at a scientific congress.

2 Introduction

The disposition of drugs in children varies from that in adults because pharmacokinetics and pharmacodynamics differ as compared to adults with huge implications on the development and use of medicines for children[1]. So far, over 60% of drugs for children are given off-license and/or off-label[2]. This has been confirmed in a recent study enrolling five European paediatric hospitals: Two thirds of the paediatric in-house patients received a medication that had no marketing authorisation in this country or in this indication[3]. Paediatric data was provided for only 15 of 110 new drugs centrally authorised by the *European Medicines Agency* in 2000 despite the fact that 49 of them involved indications of paediatric relevance[4]. But even after implementation of the Paediatric Regulation (EC) 1902/2006 in 2007, off-label drug use rate in Europe was found to be between 33.2% and 46.5% in inpatients and between 3.3% and 13.5% in outpatients[5].

Before marketing a new medicinal product for human use extensive studies are required including preclinical tests and clinical trials to ensure that it is safe, of high quality, and effective for use in the target population. The lack of trials in children and thus the lack of evidence for treatments in this population results in the administration of potentially inadequate substances and doses[1]. This leads to an increased risk of potential insufficient treatment, or adverse reactions including death, and deprives children from the full benefit of therapeutic advances. The pharmaceutical industry is showing limited interest to counteract this problem as the costs involved in obtaining a licence may never be recovered.

The current practice of administrating liquids or syrup in children results in a surprisingly unreliable dosing with substantial under- or over-dosage[6]. Thus, it is not only necessary to investigate the efficacy and optimal doses of pharmaceutical substances for different paediatric age groups but also to develop adapted galenic formulations for the most suitable routes of administration.

For these reasons, treatment of paediatric patients with drugs in hospitals is impeded by a shortage in the availability of licensed drugs in an appropriate formulation. In clinical practice, the specific paediatric requirements for adequate dosing depend on the age and physical development stage of the child, but the major deficiencies involve the availability of the required strength of formulation, the child's ability to ingest standard-size solid dosage formulations, and the taste of oral medicines. This often results in a choice of an alternative formulation e.g. liquid or suppository. Despite the importance of appropriate formulations in pharmacotherapy for children there is little factual knowledge about the use of dosage forms in current practice[7].

Availability of suitable solid oral dosage forms would have huge advantages in avoiding the problems of drug stability, potentially toxic excipients, storage conditions[2], taste-masking[8] and precise dosing that liquids account for. However, at

present there is little scientifically sound data on suitability of different formulations in children of different age groups and there are concerns and uncertainties amongst the clinicians about the age at which young children can safely swallow orally administered solids, such as conventional tablets and capsules. The understanding of the ability of children to swallow orally administered solids still seems to be based on perception rather than evidence[8]. Krause and Breitkreutz[9] published an overview of the current stage of paediatric formulation development and state: “A major challenge in drug development is paediatric drug delivery; however, the problems associated with drug administration in this population are manifold. Because of the highly heterogeneous nature of the patient group, ranging from new-borns to adolescents, there is a need to use suitable excipients and dosage forms for different age groups and suitable delivery devices for certain formulations. So far, there is a lack of suitable and safe drug formulations for children, especially for the very young and seriously ill. Current advances in paediatric drug development include interesting new drug delivery concepts such as fast-dissolving drug formulations, including buccal films and wafers, and multiparticulate dosage forms. Parenteral administration is likely to remain the first choice for children in the neonatal period and for emergency cases. Alternative routes of administration also under investigation include transdermal, pulmonary and nasal drug delivery systems. A few products are already available on the market, but others are still under development and will need further investigation and clinical proof.”

With implementation of the new *European Paediatric Regulation* 1902/2006[10] on medicinal products for paediatric use in 2007 the European and national legislators intended to create an environment for research on paediatric treatments and thus to improve the health of children in Europe by:

- facilitating the development and availability of medicines for children aged 0 to 17 years,
- ensuring that medicines for use in children are of high quality, ethically researched, and authorised appropriately,
- improving the availability of information on the use of medicines for children,

without:

- subjecting children to unnecessary trials,
- or delaying the authorisation of medicines for use in adults.

With a system of obligations and rewards for pharmaceutical industry this *Paediatric Regulation* has dramatically changed the regulatory environment for paediatric medicines in Europe: it determines that European marketing authorisation for new medications may be granted only if the sponsor company also provides data on use of the respective medication in children. In such a *Paediatric Investigation Plan* the paediatric development strategy needs to be outlined and approved by the *Paediatric Committee* at the *European Medicines Agency* (EMA) in an early clinical development stage and its completion is verified before a marketing authorisation dossier is accepted for submission to the respective competent authority. The

Paediatric Regulation also encourages the generation of paediatric data for drugs already registered for indications in adults and calls for developing suitable paediatric formulations to ensure adequate dosing and administration of the drugs.

The EMA Reflection Paper *Formulations of Choice for the Paediatric Population*[7] published in 2006 provided a summary of the current stage of knowledge on paediatric formulations and came to the conclusion: "There may be no single formulation, which is ideal for paediatric patients of all ages such that a range of dosage forms in the portfolio will be preferred. The following will be important considerations:

- minimal dosage frequency
- one dosage form fits all or a full range
- minimal impact on life style
- minimum, non-toxic excipients
- convenient, easy, reliable administration
- easily produced, elegant, stable
- cost and commercial viability"

The Reflection Paper then provided recommendation for aspects to be considered when developing new oral paediatric formulations like

- liquid formulations
- oral evervescent dosage forms
- oral powders and multiparticulate systems
- orodispersable dosage forms
- chewable tablets
- chewing gum
- tablets and capsules

and described advantages of buccal/sublingual administration (buccal and sublingual tablets or muco-adhesive preparations) as well as nasal administration (drops, spray, or powder), rectal, trans-dermal, pulmonary and parenteral administration.

It concluded that very little data is available on the suitability of the different formulations for children of different age groups but based on evidence from prescriptions for different dosage forms in relation to age, anecdotal reports of very young children being trained to manage oral solid dosage forms for chronic illness such as leukaemia and HIV and a questionnaire to 40 experts, the Reflection Paper provided a table of recommended dosage forms per age group.

As conclusion the *World Health Organization* (WHO) recommended the use of solid multiparticulates in children[11]. In contrast, the EMA questioned their applicability at an age below two years in their first version of the *Guideline on Pharmaceutical Development of Medicines for Paediatric Use*[12]. In the revised version[13] which came into force in 2014, the Guideline acknowledges that "…different solid formulations

might be age-appropriate but the acceptability of the size and shape of tablets by the target age group(s) should be justified, and where relevant supported by appropriate studies or clinical evidence. It should be noted that limited data are available in the literature regarding the influence of size, shape and the number of tablets on acceptability in different paediatric age groups."[13]

Thus there is a need for scientifically sound data to compare different oral paediatric administration routes referring to suitability and capability of children (particularly in young age) to ingest different galenic formulations to increase the safety and reliability of drug administration. In paediatric practice syrup is the most frequently used formulation. In addition, specially designed mini-tablets have advantages as they are easy in handling and a cheap alternative. Moreover, they provide advantages over liquid formulations regarding drug stability, potentially toxic excipients, and storage conditions. Thomson et al. demonstrated the suitability of 3 mm diameter mini-tablets in 5-year old children, whereas less than half of the preschool-aged children were capable of swallowing them[8].

In our pilot study on the administration of a little smaller mini-tablet of 2 mm diameter in children performed at the Paediatric Clinic of the University Hospital of Düsseldorf in 2010 with 10 children in each age group[14] we provided sufficient data to calculate the sample size of the following confirmatory study[15]. The cut-off age chosen in our study was at the age of five years as by the age of six years children have adult-like control during swallowing[16]. In our second study[15] enrolling a total of 306 children with 51 children per age group we demonstrated the suitability ("swallowed" or "chewed") of the uncoated mini-tablet in all age groups. The suitability was even superior to the syrup in most of the investigated age groups. As this superiority was also identified in children between 6 and 12 months the question aroused whether solid dosage forms could also be suitable for new-borns between 2 and 28 days. Therefore, we performed a third study with 151 new-borns[17] where we demonstrated that the suitability of mini-tablets is significantly higher than that of the syrup. Taking these results from our research group into account, the revised version of the EMA Guideline from 2014[13] has no age recommendation for solid oral dosage forms any more. As a next step it was important to demonstrate that a large number of uncoated mini-tablets can be administered to small children to achieve the application of higher doses of different medications with this dosage form. Therefore, we performed a clinical trial in 372 patients showing that the administration of 25, 100 and 400 uncoated mini-tablets in comparison to syrup is well accepted (under editorial review).

3 Rationale

Due to the lack of scientifically sound data on the suitability of bigger solid oral formulations for children of different age groups and the experiences with dosing and

stability problems with liquid formulations it is important to perform a clinical trial in a sufficiently large number of patients of the particularly vulnerable age groups, namely 1 to 5 years inclusive, comparing the acceptability, swallowability and palatability of oblong-tablets with the current standard, the syrup and the newly recommended 2 mm mini-tablets. The amount of active substance that can be administered with three 2 mm mini-tablets and 3 ml of syrup is equivalent to the amount that can be administered with one oblong-tablet of a size of 2.5x6 mm.

Acceptability, swallowability and palatability have proven to be suitable parameters to objectively assess the suitability of oral formulations for children and will allow the provision of recommendations for the most suitable oral paediatric formulations for this age group. Suitable oblong-tablets would meet targets presented in the original EMA Reflection Paper *Formulations of Choice for the Paediatric Population* [8]: a) one dosage form fitting the full range of children, b) a minimum of or only non-toxic excipients, and c) easily produced, elegant, stable drug formulations.

The main concern with oral formulations, especially in young children, is their ability to swallow solid formulations relating to the risk of inhalation and aspiration. There is very little physiological data on the development and maturation of the deglutition act in small children. This study is supposed to assess the frequency of choking on solid and liquid formulation of small children as a parameter for the maturity of the deglutition act.

The ICH E 11 guideline[18] has provided an age classification based on general considerations of developmental biology and pharmacology. However, its recommendations include the request to adapt the age categories to the current knowledge of paediatric pharmacology. This study will help to define the most suitable age categories that would have to be considered in future clinical trials with oral formulations.

To reduce the variability of data and the number of children required in this study an open, randomized, age-stratified two-way cross-over design with two parallel groups and age-stratification into four groups is chosen. The four prior studies with mini-tablets have shown that repeated administration of only placebo-containing oral formulations is acceptable for children of all age groups investigated. As no active drug is administered, blinding is not necessary to avoid observation bias and would not be practicable.

4 Ethics

4.1 Ethical Review

The final study protocol, including the final version of the Participant Information and Consent Form as well as the Assent, require a favourable opinion in writing by the

Ethics Committee of the Medical Faculty of the Heinrich Heine University Düsseldorf before the enrolment of any participant into the study. The Principal Investigator will also be responsible for seeking favourable opinion from the IEC in case of a need for any substantial amendment to the protocol.

4.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles which have their origin in the Declaration of Helsinki and which are consistent with Good Clinical Practice and applicable regulatory requirements. However, this study does not fall under the German Drug Act (*Arzneimittelgesetz, AMG*) because it does not include the application of an active investigational medicinal product as defined in the AMG. Paediatric patients participating in this study will have no direct benefit from their participation but the study imposes only minimal risk and minimal burden on the participating patients and their participation will help future children requiring adequate dosing and application of medical treatment ("group benefit").

Independent monitoring and data management of this study will be performed by the *Koordinierungszentrum für Klinische Studien* (KKS), Heinrich-Heine Universität Düsseldorf.

4.3 Participant Information Sheet and Informed Parental Consent Form

The Principal Investigator will ensure that the potential participant's parents are given full and adequate oral and written information about the nature, purpose, and possible risks and benefits of the study. Parents must also be notified that they are free to withdraw their child from the examination at any time. The parents will be given an opportunity to ask questions and get time for consideration. The participant's dated and signed Informed Parental Consent will be obtained prior to any activity related to the study. The original must be stored by the Principal Investigator. A copy of the Parent Participant Information including the signed Parental Consent Form will be given to the parents of the participant. The investigator, or designee, will note the date and time of consent completion in the participant's records. Major amendments to the protocol that affect the scope of the examination at the participant level and/or updates to the safety profile for the examination will be reflected in a revised participant information sheet and consent form.

A sample Participant Parental Information Sheet and Informed Parental Consent Form is enclosed (Appendix A).

4.4 Assent

The children will be informed about the study procedures, risks and benefits of their participation as far as the comprehension of the child allows, using a comic

explaining the procedure. Their assent will be sought and documented by the investigator.

Appendix B provides an example of the child information sheet.

4.5 Participant Liability Insurance

Adaequate participant liability insurance coverage will be provided by Zurich Versicherung AG, Poppelsdorfer Allee 25-33, 53115 Bonn.

5 Objectives

5.1 Primary Objectives

To demonstrate non-inferiority in acceptability of the oblong-tablet in comparison to 3 ml glucose syrup in children aged between 1 year and 5 years inclusive.

5.2 Secondary Objectives

To demonstrate non-inferiority in acceptability of the oblong-tablet in comparison to three mini-tablets in children aged between 1 year and 5 years inclusive.

To compare swallowability of the oblong-tablet and of 3 ml glucose syrup in children aged between 1 year and 5 years inclusive.

To compare swallowability of the oblong-tablet and of three mini-tablets in children aged between 1 year and 5 years inclusive.

To compare acceptability of an oblong-tablet and of 3 ml glucose syrup in subsets of children aged 1 to 2 years, 2 to 3 years, 3 to 4 years, 4 to 5 years and 5 to 6 years.

To compare acceptability of an oblong-tablet and of three mini-tablets in subsets of children aged 1 to 2 years, 2 to 3 years, 3 to 4 years, 4 to 5 years and 5 to 6 years.

To compare swallowability of an oblong-tablet and of 3 ml glucose syrup in subsets of children aged 1 to 2 years, 2 to 3 years, 3 to 4 years,4 to 5 years and 5 to 6 years.

To compare swallowability of an oblong-tablet and of three mini-tablets in subsets of children aged 1 to 2 years, 2 to 3 years, 3 to 4 years, 4 to 5 years and 5 to 6 years.

To compare the palatability of an oblong-tablet, three mini-tablets and 3 ml syrup in each age group.

To identify any possible problem that could occur during deglutition.

To identify the percentage of children who inhaled or coughed during ingestion of any of the oral placebo formulations.

To investigate the safety of the oral placebo formulations.

To investigate the percentage of approached parents consenting to participation of their child in this study.

To identify reasons why approached parents are not willing to agree to the participation of their child in this study.

6 Examination Plan

6.1 Design

This study will be performed in two parallel groups (study arms) in a single-centre, open, randomised, single dose, two-way cross-over design with age-stratification into four groups. The children will be stratified into the following five age sub-groups: 1 to < 2 years, 2 to < 3 years, 3 to < 4 years, 4 to < 5 years and 5 to < 6 years. Each age sub-group will have two parallel groups: The first group will receive one oblong-tablet and 3 ml glucose syrup in the order assigned by randomisation. The second group will receive one oblong-tablet and three 2 mm mini-tablets in the order assigned by randomisation.

6.2 Population

6.2.1 Source and Number of Participants

The children (inpatients or outpatients) will be recruited in the Department of General Paediatrics, Neonatology and Paediatric Cardiology of the University Hospital Düsseldorf, Germany. For the study a total of 280 evaluable children (140 children per parallel group (study arm), 28 children per age group) will be required. To ensure 192 evaluable children it is assumed that the parents of 600 children will have to be approached.

6.2.2 Inclusion Criteria

1. Age
Children aged from 1 to 5 years inclusive

2. Sex
Male and female

3. Recruiting

Recruiting will take place in the Paediatric Clinic of University Hospital Düsseldorf (inhouse and outpatient).

4. Health
Based on medical history, physical examination and all other appropriate diagnostic procedures they are able to swallow.
Participants suffering from illness must be able to swallow the three formulations and to accept the study procedures. This conclusion is based on medical history, physical examination and all other appropriate diagnostic procedures.

5. Compliance
Participants and participants' parents understand and are willing, able and likely to comply with examination procedures and restrictions.

6. Consent
Participant and/or participant's parents are capable of understanding the examination procedures, participant obligations as well as risks and benefits of participation in this study and have given written informed consent and assent where possible.

6.2.3 Exclusion Criteria

1. Disease/Illness
Any impairment of swallowing either solids or glucose-syrup as a consequence of

a) chronic illness (e.g. cerebral palsy)
b) acute illness (e.g. sepsis, respiratory distress, gastroenteritis, respiratory tract infection)
c) oral deformation

2. Intolerance
Lactose-Intolerance

3. Pre- and Concomitant Medication
Any drug that causes nausea, fatigue or palsy.

4. Intervention
No examination shortly after surgical intervention until child is allowed to drink and capable to follow the study-related instructions.

5. Nutrition
Children, who have eaten one hour before examination and who afterwards feel sick.

6.2.4 Participants Withdrawal Criteria

Participants and participants' parents have the right to withdraw from the examination at any time for any reason. The investigator also has the right to withdraw

participants from the examination in the event of intercurrent illness or adverse events, after an interfering prescribed procedure, protocol deviations, administrative or other reasons. It is understood by all concerned that an excessive rate of withdrawals can render the examination uninterpretable; therefore, unnecessary withdrawal of participants should be avoided. Should a participant decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible. A complete final evaluation at the time of the participant's withdrawal will be made with an explanation of why the participant is withdrawing from the examination.

If the reason for the withdrawal of a participant from the examination is an adverse event, the adverse event will be recorded in the case report form "(CRF)' and marked as reason for withdrawal.

6.2.5 Participants Replacement

Randomised participants who withdraw from the examination at any stage will be replaced receiving the successive randomisation number.

6.2.6 Participants Restriction

Participants are asked to avoid eating within one hour before the clinical trial.

6.3 Clinical Supplies

6.3.1 Formulations for the Study

Participants will be given two of the three following formulations in a randomised fashion:

A) Oblong-tablet 2,5 x 6 mm uncoated: 1 per child and intervention
B) Mini-tablet ø 2 mm uncoated: 3 per child and intervention
C) Glucose-Syrup 15%: 3 ml per child and intervention

A) Manufacturer: NextPharma PHARBIL Waltrop GmbH
Im Wirrigen 25, 45731 Waltrop
Ingredients: Lactose, cellulose, magnesium stearate and anhydrous colloidal silicon dioxide

B) Manufacturer: NextPharma PHARBIL Waltrop GmbH
Im Wirrigen 25, 45731 Waltrop
Ingredients: Lactose, cellulose, magnesium stearate and anhydrous colloidal silicon dioxide

C) Manufacturer: Caesar & Loretz GmbH
Herderstraße 31, 40721 Hilden

Ingredients: Glucose 250g
Water 37,5g

6.3.2 Packaging and Labelling

Oblong-tablets and mini-tablets will be provided as bulk in a plastic bag.
The glucose-syrup will be delivered in plastic bottles.

6.3.3 Accountability of Examination Supplies

All material supplied will be for use only in this study and will not be used for any other purpose.

The investigator or designee will maintain a full record of formulation accountability. A Formulation Dispensing Log must be kept current and will contain the following information:

- the identification of the participant to whom the formulation was dispensed;
- the date and type of the formulation dispensed to the participant.

The order of administration will be recorded in the CRF by the investigator. Administration of the two oral placebo formulations will be supervised by the investigator, who will ensure that the formulations have been swallowed via observation of the deglutition and a visual inspection of the mouth. The Formulation Dispensing Log will be signed attesting that the formulations were administered correctly.

At the end of the examination, the amount of the remaining supplies will be verified and then destroyed.

6.3.4 Storage of Clinical Supplies

Clinical supplies must be stored in compliance with the label requirements at room temperature between 15°C - 25°C in a secure, locked, dry area away from direct sunlight.

6.3.5 Precautions

No special precautions are necessary, provided the examination is conducted according to this protocol.

6.4 Examination Schedule

6.4.1 Selection and Screening Phase

Potential participants and their parents will be contacted in the Paediatric Clinic of the University Hospital Düsseldorf during their inhouse or outpatient stay based on a

referral from their treating physician in the hospital. If the children and/or their parents are interested in participation the children and their parents will be invited to an informed consent session during which the principal investigator or his designee will discuss the details of the examination: potential participants and their parents will be provided with written and oral information about the examination as well as the risks and benefits of participation. They will be given adequate time to read and consider the information provided and to ask questions. If the participant and the parents wish to participate in the study, the child's both parents will be required to give written informed consent and the children their assent as far as possible before any study-related procedures will be performed.

6.4.2 Participant Numbering Procedure

Once the parents have given informed consent the participants will be allocated a unique identifying number consisting of the sequence of enrolment presented in a Participant Identification Log.

6.4.3 Randomisation Procedure

280 children, male and female, aged from 1 to 5 years will be recruited. They will be randomly allocated to one of two parallel groups (140 children per parallel group). Group 1 will receive one oblong-tablet and 3 ml syrup in a randomised order. Group 2 will receive one oblong-tablet and three mini-tablets in a randomised order. Each group will be stratified into four age groups:

1. 1 - < 2 years
2. 2 - < 3 years
3. 3 - < 4 years
4. 4 - < 5 years
5. 5 - < 6 years

In the study each stratum will contain 28 children. There will be no fixed ratio between male and female children per age group as no sex-related differences in acceptability of galenic formulations under investigation are expected.

Randomisation within each age group will be performed as follows:

At first, when the child has been assessed as eligible for the trial, it will be randomized to one of the two study arms A or B:

A: Children will receive one oblong-tablet and 3 ml glucose syrup in the order assigned by randomisation.

B: Children will receive one oblong-tablet and three 2 mm mini-tablets in the order assigned by randomisation.

Randomisation will be provided for at least 300 participants as drop-outs will have to be replaced. Replacing participants will receive the next available randomisation number.

6.4.4 Examination Phase

The child and the parent(s) will be seated in a quiet, distraction-free area. The Investigator will review all provided information and perform the judgement on the child's suitability for the study. Parents will be asked detailed information about the child's medical history to ensure that all inclusion and exclusion criteria are fulfilled and an oral inspection will take place using a tongue depressor.

All information and instructions will be given in a standardised manner by the investigator in an age-appropriate language.

6.4.4.1 Application and Assessment

The solid formulations and the glucose-syrup are to be taken by mouth.
In the first part of the examination the placebo formulation requested by the randomisation scheme will be applied:
The oblong-tablet will be placed on the tongue and the child will be asked to put the tongue back into the mouth. The participant has to swallow the oblong-tablet with up to three mouthfuls of a drink of his/her choice.

The three mini-tablets will be placed on the tongue and the child will be asked to put the tongue back into the mouth. The participant has to swallow the mini-tablets with up to three mouthfuls of a drink of his/her choice.

The glucose syrup is given with a syringe in a slightly opened mouth. The glucose syrup has to be swallowed with up to three mouthfuls of a drink of his/her choice.

The deglutition process and the child's reactions will be thoroughly observed by the investigator and video documented. 45 seconds after placing of the oblong-tablet, mini-tablets or syrup into the child's mouth the mouth will be inspected by the investigator and the result as well as the results of the observation of the deglutition process and child's reactions assessed according to the criteria described in Section 7.1 "Evaluation Variables" and recorded in the specially prepared shadow source document.

In the second part the process will be repeated with the other formulation within 15 minutes.

The palatability of the formulations will be assessed by video documentation of the application and physical reactions in the following seconds. From this video sequence approximately 45 seconds from the application onwards will be cut out. The other material will be deleted irrevocably. Those two sequences per patient (application of the oblong-tablet and application of the syrup or application of the oblong-tablet and application of the mini-tablets) will be saved pseudonymously. The videos will not be accessible to third parties. The video material will not be published.

Possible exceptions, e.g. for presentations on international conferences, must be permitted by both parents separately. The videos will be evaluated independently by two blinded raters who are liable to the medical confidentiality. After the publication of the results in an international journal, at the latest after 10 years, the videos will be deleted irrevocably. At any time for any reason participant´s parents are free to ask for the deletion of the video material, also after the above mentioned separate agreement.

Any adverse events observed and reported will be documented and assessed according to the criteria described in Section 7.2 “Safety Variables”.

In case of any possible medical problems during deglutition, a physician will be available in short delay as the physiological examination will take place in the Paediatric Clinic of University Hospital Düsseldorf.

The total study duration will not exceed 18 months.

7 Evaluation Criteria

7.1 Evaluation Variables

7.1.1 Acceptability and Swallowability:

7.1.1.1 Oblong-tablet and Mini-tablets:

- Swallowed
    - which implies that no chewing took place during deglutition and no residuals of the solid were found during oral inspection
    - interpreted as accepted and swallowed
- Chewed
    - which implies that chewing was observed before deglutition or that the whole or parts of the solid were found during oral inspection
    - interpreted as accepted but not swallowed
- Spat out
    - which means that no deglutition took place and that the solid is no longer in the child’s mouth
    - interpreted as not accepted and not swallowed
- Choked on
    - which means that the solid was swallowed the wrong way or that a cough was caused
    - interpreted as not accepted and not swallowed
- Refused to take
    - which implies that the child didn’t allow the investigator to place the solid in the mouth
    - interpreted as not accepted and not swallowed

7.1.1.2 Glucose-syrup:

- Everything swallowed
    - which means that no liquid was left in the mouth and no drops left the mouth
    - interpreted as accepted and swallowed
- Small runlet flowing out of the mouth or leftover in the syringe
    - which means that the child did not swallow completely
    - interpreted as accepted but not swallowed
- Spat out
    - which means that no deglutition took place because the child disgorged the glucose syrup directly
    - interpreted as not accepted and not swallowed
- Choke on
    - which means that the syrup was swallowed the wrong way or that a cough was caused
    - interpreted as not accepted and not swallowed
- Refused to take
    - which implies that the child didn't allow the investigator to place the syringe in the mouth or that the child didn't close the mouth correctly and that all glucose syrup was leaking out of the mouth because no deglutition took place
    - interpreted as not accepted and not swallowed

7.1.2 Palatability:

After placing the formulation into the child's mouth, the immediate physical reactions of the child will be carefully observed by videotaping. The video material will be evaluated by two blinded, independent experienced and trained raters, and the child´s reaction will be rated according to the following criteria:

	Criterion	**Interpretation**	**Description of Reaction**
①	Pleasant	Positive hedonic pattern	Tongue protrusion, smack of mouth and lips, finger sucking, corner elevation
②	No change	Neutral	Neutral mouth movements (irregular and involving lips)
③	Unpleasant	Negative aversive pattern	gape, nose wrinkle, eye squinch, frown, grimace, head shake, arm flail

7.2 Safety Variables

7.2.1 Possible Risks

As the formulations do not contain any active ingredient but only standard ingredients of placebo formulations, respectively a pure glucose solution, there will only be minimal risks of adverse events to be expected. Only lactose intolerance or allergic reactions related to any of the other standard ingredients might become a problem in children not known to suffer from this intolerance.

Aspiration, especially in the younger age groups, poses a certain level of risk, however, during the four previous studies with uncoated mini-tablets performed in 2010, 2011, 2013/2014 and 2015 with in total more than 800 children no single case of aspiration was observed. Due to the fact, that oblong-tablets are bigger than mini-tablets, the lowest age investigated in this trial is 1 year. An additional safety factor is the fact that the oblong-tablets and the mini-tablets are uncoated and therefore are soluble in the mouth within seconds. Yet, all possible efforts will be made to minimise this risk: the study will take place in the Paediatric Clinic of University Hospital Düsseldorf where all emergency treatment options will be available on short notice. The investigators are prepared and trained to handle the situation adequately.

7.2.2 Adverse Events

All adverse events encountered during the study, whether spontaneously reported by the participant or his/her parent at any time during the examination or elicited by the investigator or a member of the team in a standard manner, will be reported in the CRF.

The investigator or designee must ask the participant's parent(s) the following question after each examination: "*Does your child feel unwell or has your child experienced any symptoms?*"

All adverse events encountered during the study will be reported in the CRF. An Adverse Event (AE) is any untoward medical occurrence in a participant administered any of the oral formulations and which does not necessarily have to have a causal relationship with formulation administration. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of an oral formulation, whether or not considered related with the application. Furthermore, any unintended event (including physiological, psychological or behavioural change) from the time a participant's parents have given informed consent, including intercurrent illness, will be documented and assessed.

Adverse events will be described by diagnosis and not by symptoms when possible (e.g. cold, seasonal allergies, etc. instead of runny nose).

Adverse events will be graded on a three-point scale and reported in detail as indicated in the CRF:

- mild – easily tolerated, causing minimal discomfort and not interfering with normal everyday activities
- moderate – sufficiently discomforting to interfere with normal everyday activities
- severe – incapacitating and/or prevents normal everyday activities.

Causal relationship of each adverse event should be assessed according to one of the following criteria by the investigator:

- Not related – The event is clearly related to other factors such as the participant's clinical state, therapeutic interventions, or concomitant medications administered to the participant
- Unlikely – The event was most likely produced by other factors such as the participant's clinical state, therapeutic interventions, or concomitant medications administered to the participant; **and** does not follow response pattern to the oral formulation
- Possible – The event follows a reasonable temporal sequence from the time of administration; **and/or** follows a known response pattern to the oral formulation; **but** could have been produced by other factors such as the participant's clinical state, therapeutic interventions, or concomitant medications administered to the participant
- Probable – The event follows a reasonable temporal sequence from the time of administration; **and** follows a known response pattern to the oral formulation; **and** cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions, or concomitant medications administered to the participant.
- Highly Probable – The event follows a reasonable temporal sequence from the time of administration; **and** follows a known response pattern to the oral formulation; **and** cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions, or concomitant medications administered to the participant; **and** either occurs immediately following administration, **or** improves on stopping oral formulation, **or** reappears on repeat exposure, **or** there is a positive reaction at the application site.

7.2.3 Serious Adverse Events

Any clinical adverse event, that is serious (as defined below) occurring during the course of the study, irrespective of the formulation treatment received by the participant, must be reported to the Principal Investigator within 24 hours (or sooner if possible) of the investigator or study staff becoming aware of the situation.

A serious adverse event is any adverse experience occurring that results in any of the following outcomes:

- Death
- Life threatening (places the participant, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred, i.e., it does not include an adverse experience that, had it occurred in a more severe form, might have caused death)
- Persistent or significant disability/incapacity (disability is a substantial disruption of a person's ability to conduct normal life functions);
- Permanent disability;
- Participant hospitalisation or prolongation of hospitalisation;

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

The term 'severe' is a measure of intensity; thus a severe adverse event is not necessarily serious. For example, nausea of several hours duration may be rated as severe but may not be clinically serious.

For all suspected unexpected serious adverse reactions (SUSARs), the investigator must inform the Ethics Committee of the University of Düsseldorf within 7 days, assessed and documented by the following details: date of onset, date ceased, frequency, intensity, action taken, and outcome to date.

Such preliminary reports will be followed within 15 days by detailed descriptions later which will include copies of hospital case reports, autopsy reports and other documents when requested and applicable.

The Principal Investigator will decide which SAE's have to be considered SUSAR's and will ensure the report of the SUSAR to the Ethics Committee.

8 Statistical Evaluation

8.1. Statistical methods

The statistical analysis will be performed separately for each study arm (oblong-tablet in comparison to syrup and oblong-tablet in comparison to mini-tablets) of this trial.

Demographic data and baseline characteristics will be summarised descriptively by sequence group and overall. Efficacy and safety data will be summarised descriptively by treatment. Descriptive statistics will also be presented broken down by age groups. Categorical data will be summarised by frequencies and percentages,

continuous data by number of observations, means, standard deviation, minimum, first quartile, median, third quartile and maximum.

The primary outcome of acceptability will be analysed as binary outcome by combining the first two acceptability categories (swallowed / chewed for the tablets or everything swallowed / small runlet for syrup, respectively) as “accepted” and the three remaining acceptability categories as “not accepted”.

The acceptability will be compared between both treatments by applying the analysis proposed by Schouten and Kester[19]. At first, the difference in acceptability rates of the oblong tablet versus the reference product will be estimated for each sequence group and then averaged over both sequence groups in a second step. Corresponding one-sided 97.5% confidence intervals will be calculated for the averaged difference of acceptability rates.
The oblong-tablet will be considered as non-inferior in comparison to the reference product, if the lower limit of the one-sided 97.5% confidence interval for the averaged difference in acceptability rates (pOblong-tablet - pReference) exceeds -15%-pts.
The corresponding hypotheses to be tested are:
H0: πOblong-tablet ≤ πReference – 15% versus H1: πOblong-tablet > πReference – 15%,
where π denoted the true probability for acceptance.

If non-inferiority of the oblong tablet to reference could be concluded, then superiority could be tested subsequently. Superiority could be concluded if the one-sided 97.5% confidence interval for the difference in acceptability rates (pOblong-tablet - pReference) does not include zero.

Frequencies of acceptability (“accepted” / “not accepted”) will be tabulated by treatment. Moreover, 2x2 contingency tables will be provided presenting paired samples (i. e. result after Oblong-tablet versus result after reference).

Similar analyses as described above will also be performed for each of the five age groups in exploratory manner.

The secondary outcomes of swallowability and palatability will also be analysed as binary outcome and the analyses will be performed analogously to the analysis of acceptability.

8.2. Sample size calculation

The sample size required to meet the primary objective is based on an acceptance rate of the syrup of 80% as observed in our previous clinical studies. Furthermore, the following assumptions are made:

Non-inferiority margin: 15%-pts
Significance level: α = 2.5% (one-sided)
Power: 90%
Correlation: r=0.3
Sample size calculation results to a total number of 132 evaluable cases.
Since this design is stratified by 5 age groups, and each age group has to be balanced by treatment sequence, 140 children are required for the study arm with syrup as reference (i.e. 28 children per age group).

With regard to the secondary objective (to demonstrate non-inferiority in acceptability of the oblong-tablet in comparison to three mini-tablets), the acceptance rate of the mini-tablet is expected to be higher than 80% (up to 90%). Thus, less children would be needed. However, a sample size of 140 children will be chosen as in the other study arm to get a more precise estimate of the acceptability rates in the age groups.

Thus, both study arms need to include 280 children in total

9 Documentation, CRFs, and Record Keeping

9.1 Trial Master File/Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the examination to be fully documented and the examination data to be subsequently verified. These documents should be classified into two different categories (1) trial master file, and (2) participant clinical source documents.

The trial master file will contain the protocol/amendments, sample and completed case report and query forms, favourable IEC opinion, sample of the patient information sheet/informed consent form and assent, all pertinent documentation on study medication, staff curriculum vitae and training records, as well as authorisation forms and other appropriate documents / correspondence, etc. as defined in ICH-GCP(R2) under Appendix VIII “Essential documents”.

The date and time of the patient’s participation in the study will be documented in the patient’s hospital record together with the date and time of informed consent signature and a short description of the course of the examination and safety observations. For each participant a participant study file will be prepared containing the signed informed consent, a paper version of the electronic CRF (eCRF) to be used as shadow source document as far as possible. Other documents in this participant study file will include certified copies of relevant participant hospital/clinic records, physician’s and nurse’s notes, as well as special assessment reports, physician’s letters, etc. These two categories of documents must be kept on file by the Principal Investigator according to the requirements of the Paediatric Clinic of University Hospital Düsseldorf (for 10 years). The Principal Investigator is also

required to keep the Participant Screening and Identification Logs on file for at least 10 years after completion or discontinuation of the examination.

The contact details of all parents who will be approached for study participation will be collected in a parents contact table, a unique number per child assigned, agreement to participation noted and reasons for refusal documented. After completion of the study the contact details of all parents who refused participation will be destroyed so that only anonymised data related to their reason for refusal remain.

No document should be destroyed without a prior written approval of the Principal Investigator. Should the Principal Investigator wish to assign the examination records to another party or move them to another location, the Paediatric Clinic of University Hospital Düsseldorf must be notified in advance.

If the Principal Investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Principal Investigator and Paediatric Clinic of University Hospital Düsseldorf to store these in a sealed container(s) outside of the site so that they can be returned sealed to the Principal Investigator. Where source documents are required for the continued care of the participant, appropriate copies should be made for storing outside of the site.

9.2 Case Report Forms (CRFs)

For each participant who has given informed consent, an electronic CRF will be completed and electronically signed by the Principal Investigator to certify that the data within each eCRF are complete and correct. If a participant is withdrawn from the examination because of an adverse event, thorough efforts should be made to document the outcome.

All forms should be filled out during (or immediately after) a participant assessment and must be complete, attributable, and legible. Errors should be crossed out, but not obliterated or covered with correction fluid, the correction inserted, and the change initialled and dated by the investigator or his/her designee.

9.3 Data Handling

The data management will follow a Remote Data Entry approach. The electronic Case Report Form (eCRF) will be implemented in a modern Clinical Data Management System (CDMS) with Electronic Data Capture functionality (EDC) available at the KKS Düsseldorf. The system complies with the relevant international standards and provides the capability to perform the major data management activities within a consistent, auditable and integrated electronic environment (query management, data entry, data validation). The data will be collected primarily on shadow paper CRFs, which will be transcribed to the eCRF by the site personnel

(investigator or assistant personnel). The query management will be performed electronically. Any queries arising from data entry will be checked with the investigator and corrections approved. The database will be checked for internal consistency and critical data compared with the shadow paper CRFs.
The collected data that are transferred to the data management centre will only include pseudonymised data. The connection is secured by SSL-technology. Archiving of the clinical database including the audit trail will be provided by the data management centre in a machine independent format. The Principal Investigator will be provided with a copy of all completed electronic CRF of the participants at study termination. After database lock data will immediately be imported into standard statistical software systems.

10 Conditions for Substantial Amendments

Modifications to the protocol which could potentially adversely affect the safety of participants or alter the scope of the investigation, the scientific quality of the examination, the experimental design, frequency of administration, assessment variables, the number of participants enrolled, or participant selection criteria must be made only after appropriate consultation between the Principal Investigator and Professor Dr. Jörg Breitkreutz, Institut für Pharmazeutische Technologie und Biopharmazie.

Substantial amendments will be submitted by the Principal Investigator to the local Ethics Committee for favourable opinion. Non-substantial amendments will be filed in the Trial Master File.

11 Conditions for Terminating the Study

The Principal Investigator reserves the right to terminate the study at any time. Should this be necessary, the procedures will be arranged after review and consultation by the Principal Investigator and Professor Dr. Jörg Breitkreutz, Institut für Pharmazeutische Technologie und Biopharmazie. In terminating the examination, the Principal Investigator will assure that adequate consideration is given to the protection of the participants' interests.

12 Confidentiality of Examination Documents and Participant Records

The Principal Investigator must assure that the participants' data protection rights will be maintained. On eCRFs or other documents submitted to the KKS Düsseldorf or the external statistics provider M.A.R.C.O GmbH & Co KG, participants will not be identified by their names, but by an identification code.

The Principal Investigator will keep a Participant Identification Log containing participants' identifying number, names and addresses. Documents not for submission to KKS Düsseldorf, e.g. participants' written consent forms, will be maintained by the Principal Investigator in strict confidence.

13 Publication of Data and Protection of Trade Secrets

This study is presented in the "Deutsches Register Klinischer Studien" and in the „Study Register of the Medical Faculty of the Heinrich-Heine-University" and will be subject to a doctoral thesis. The results will be reported in form of a publication in a well-established journal and in form of a poster or presentation at a scientific congress. We will report our data in accordance with the *Reporting of Noninferiority and Equivalence Randomized Trials – An Extension of the CONSORT Statement* [Piaggio 2006][20].

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6.2 Information for parents

Teilnehmerinformation

für

„Randomisierte, einfach dosierte cross-over Studie in zwei parallelen Gruppen zur Untersuchung der Akzeptanz, Schluckbarkeit und Schmackhaftigkeit von drei oralen Plazebo-Formulierungen bei kleinen Kindern“

Sehr geehrte Eltern,

für viele Medikamente, die kranken Kindern helfen, haben die Ärzte keine wissenschaftlichen Informationen darüber, welches eigentlich die beste Darreichungsform für Kinder verschiedener Altersgruppen ist, damit die Kinder ihre Medikamente auch zuverlässig schlucken. Das wurde meistens nicht systematisch untersucht. Daher gibt es auch oft keine richtig gut geeigneten Darreichungsformen speziell für Kinder. Das muss dringend geändert werden, um die Behandlung von Kindern zuverlässiger und sicherer zu machen. Hier in der Klinik für Allgemeine Pädiatrie der Universitätsklinik Düsseldorf möchten wir versuchen, durch die Mithilfe Ihres Kindes eine altersgerechte Darreichungsform für Medikamente für Kinder zu finden. Es sollen dabei jedem Kind eine Oblongtablette (längliche Tablette) und drei Minitabletten oder eine Oblongtablette und eine kleine Menge eines Glukosesirups verabreicht werden – alles ohne echte Wirkstoffe – um vergleichen zu können, welche Darreichungsform von Ihrem Kind am besten akzeptiert wird.

Vor welchen Herausforderungen stehen wir?

Ein Problem ist, dass Sirups keine lange Haltbarkeit haben, wenn die Flasche mal geöffnet wurde. Außerdem werden Sirups von Kindern oft wegen des Geschmacks abgelehnt. Daher sollte versucht werden, geschmacks-neutrale und besser haltbare Darreichungsformen für Kinder zu entwickeln. Ein weiteres Problem ist, dass viele heute in der Behandlung von Kindern eingesetzte Tabletten nicht in altersgerechten Größen und Dosierungen hergestellt werden können. Dadurch müssen herkömmliche Tabletten gebrochen oder gemahlen werden, um kleinere, für Kinder geeignete Mengen, zu erhalten. Dieses Vorgehen birgt die Gefahr, dass die gewünschte Dosis sehr ungenau ist, d.h. es kann zu einer Über- oder Unterdosierung kommen. Außerdem sind diese Bruchstücke vor allem für kleine Kinder schwierig zu schlucken. Eine mögliche Lösung stellen die bereits vor Kurzem entwickelten kindgerechten Minitabletten und die nun neu entwickelten Oblongtabletten dar, die beide eine genaue Dosierung erlauben, zuverlässig geschluckt werden können und die den bisher eingesetzten Sirup ablösen könnten.

Die klinische Studie

In dieser wissenschaftlichen Untersuchung soll nun erforscht werden, ob Kinder zwischen dem 1. und 6. Geburtstag in der Lage sind, diese speziell für Kinder entwickelten Oblongtabletten genauso gut oder sogar besser schlucken zu können als drei Minitabletten oder einen Sirup und welche der Darreichungsformen sie eher akzeptieren sowie welche Darreichungsform für welche Altersgruppe am geeignetsten ist.

Ablauf der Untersuchung

Wenn Sie in eine Teilnahme an dieser Untersuchung nach ausführlicher Aufklärung eingewilligt haben, wird Ihr Kind an zwei Schluckversuchen innerhalb von 15 Minuten teilnehmen. Zunächst wird ihr Kind über eine vom Computer erstellte Zufallsliste einer der beiden Studiengruppen zugeteilt. Je nach Gruppe erhält Ihr Kind dann entweder eine Oblongtablette und Sirup oder eine Oblongtablette und drei Minitabletten. Die Reihenfolge der verabreichten Dosierungsformen wird dabei ebenfalls vom Computer festgelegt.

Ihr Kind sollte eine Stunde vor Beginn der Untersuchung nichts gegessen haben.

Ihrem Kind werden die 3 ml eines nur Glukose enthaltenden Sirups mit einer Pipette verabreicht. Die Oblongtablette hat eine Größe von 2,5 x 6 mm, die Minitabletten haben einen Durchmesser von jeweils 2 mm. Diese beiden Tablettenarten enthalten keinen Medikamenten-Wirkstoff (Placebo), sondern bestehen nur aus verschiedenen bei der Herstellung von Tabletten üblicherweise verwendeten Zuckern. Diese beiden Tablettenarten lösen sich sehr schnell im Mund auf. Ihrem Kind werden die Oblongtablette oder die Minitabletten auf die Zunge gelegt und es soll dann die Tabletten mit einem Getränk Ihrer Wahl hinunterschlucken. Durch den Speichel und das Getränk lösen sich die Tabletten rasch, oft schon im Mund, auf.

Sobald das Kind bereit ist für den zweiten Schlucktest, wird die jeweils andere geplante Darreichungsformen verabreicht.

Vor und nach jedem Schlucktest wird der Untersucher, soweit möglich, Ihrem Kind in den Mund schauen, um zu überprüfen, ob der Mund leer ist.

Der Untersucher wird alle Beobachtungen sorgfältig dokumentieren. Außerdem werden die beiden Schlucktest videodokumentiert. Die Auswertung der erhobenen Daten erfolgt am Koordinierungszentrum für Klinische Studien der Universität Düsseldorf.

Vorteile und Risiken

In einem persönlichen Gespräch werden Sie über die Vorteile und möglichen Risiken sowie den genauen Ablauf der Untersuchung ausführlich aufgeklärt. Ihr Kind selbst hat keinen Vorteil von der Teilnahme an dieser Untersuchung, da ja kein Wirkstoff in den Darreichungsformen enthalten ist, aber dafür birgt diese Untersuchung auch nur minimale Risiken und bedeutet nur eine ganz geringe Belastung für Ihr Kind. Aber Sie helfen damit, dass wir für Millionen kranker Kinder in Zukunft besser wissen, welche Darreichungsform zuverlässig und akzeptabel ist.

Zu den möglichen Risiken zählt, dass sich Ihr Kind verschlucken und dabei sogar Atemnot entwickeln könnte oder dass es zu einer allergischen Reaktion auf einen der Zucker-Inhaltsstoffe kommen könnte. Allergische Reaktionen auf Zuckerstoffe sind extrem selten. Die Untersucher sind aber auf diese Möglichkeiten vorbereitet und können schnell helfen. Außerdem findet die Untersuchung in der Kinderklinik statt, sodass im Notfall auch sofort spezielle ärztliche Hilfe sichergestellt werden kann. Für alle Fälle wird für die Kinder in dieser Untersuchung eine Versicherung bei der Zurich Gruppe (Poppelsdorfer Allee 25-33, 53115 Bonn, Nr. des Versicherungsscheins *folgt*) in Höhe von € *folgt* pro Kind abgeschlossen, die mögliche Kosten von erforderlichen Behandlungen solcher sehr seltenen Notfälle abdeckt.

Ihr Einverständnis

Wir bitten Sie, uns Fragen zu Vorerkrankungen Ihres Kindes zu beantworten, um die Eignung Ihres Kindes für die Teilnahme an dieser Untersuchung beurteilen zu können.

Des Weiteren bitten wir Sie um Ihr Einverständnis, Ihrem Kind zwei der drei oben genannten Darreichungsformen verabreichen zu dürfen. Dies würde an einem Tag innerhalb von 15 Minuten geschehen.

Sämtliche personenbezogenen Daten werden nicht an Dritte weitergegeben.

Wenn Sie sich für die Teilnahme Ihres Kindes an dieser Untersuchung entscheiden, bestätigen Sie durch Ihre Unterschrift unter der Einverständniserklärung schriftlich, dass Sie in die Teilnahme Ihres Kindes einwilligen.

6.3 GCP Certificate

ZERTIFIKAT

Frau Juliane Münch

hat an dem Web-Seminar*

GCP-Grundkurs

am Donnerstag 28. Januar 2021 teilgenommen.

Veranstalter:
Koordinierungszentrum für Klinische Studien Düsseldorf

Eine Lernerfolgskontrolle wurde durchgeführt.

Henrike Kolbe
Kommissarische Leitung KKS Düsseldorf

*Der Kurs wurde aufgrund des Kontaktverbots im Zuge der COVID-19-Pandemie als Web-Seminar durchgeführt. Die Anwesenheit der Teilnehmer wurde per Videokonferenz und durch Zwischenfragen mit namentlichem Aufruf sichergestellt.

Fortbildung GCP-Grundkurs

Das Curriculum der Bundesärztekammer für den GCP-Grundkurs beinhaltet insgesamt 8 Unterrichtsstunden (a 45 min.) mit den folgenden Mindestanforderungen:

Thema	**Unterrichtsstunden**
Ethische Grundlagen	1
Rechtliche Grundlagen	1
Methodische Grundlagen	1
Aufklärung und Einwilligung	1
Reguläre Durchführung	3
Unerwünschte Ereignisse; Sicherheit	1
Lernerfolgskontrolle	
Gesamt	**8**

6.4 Consent and assent

Einwilligungserklärung

Teilnahme an

„Randomisierte, einfach dosierte cross-over Studie in zwei parallelen Gruppen zur Untersuchung der Akzeptanz, Schluckbarkeit und Schmackhaftigkeit von drei oralen Plazebo-Formulierungen bei kleinen Kindern“

Name des Kindes: .....

Geburtsdatum des Kindes: .....

Nach umfassender Information über die Untersuchung willige(n) ich / wir ein, dass mein / unser Kind daran teilnimmt. Über Wesen, Bedeutung und Tragweite der Untersuchung wurde(n) ich / wir informiert.

Die Entscheidung zur Teilnahme an der Untersuchung beruht auf Freiwilligkeit und kann jederzeit ohne Angabe von Gründen oder Inkaufnahme von Nachteilen beendet werden. Dies gilt auch dann, wenn ich / wir bereits die Unterschrift auf dieser Einwilligungserklärung geleistet habe(n). Wir Eltern erhalten eine Kopie des unterschriebenen Aufklärungs- und Einwilligungsschreibens. Für Rückfragen steht auch die Untersuchungsleiterin, Frau Dr. med. Viviane Klingmann, jederzeit zur Verfügung.

Einwilligungserklärung zum Datenschutz

Datenschutz:

Mir ist bekannt, dass bei dieser klinischen Studie personenbezogene Daten, insbesondere medizinische Befunde über mein Kind sowie Videoaufzeichnungen erhoben, gespeichert und ausgewertet werden sollen. Die Verwendung der Angaben über seine Gesundheit erfolgt nach gesetzlichen Bestimmungen und setzt vor der Teilnahme an der klinischen Studie folgende freiwillig abgegebene Einwilligungserklärung voraus, das heißt ohne die nachfolgende Einwilligung kann mein Kind nicht an der klinischen Studie teilnehmen.

1. Ich erkläre mich damit einverstanden, dass im Rahmen dieser klinischen Studie personenbezogene Daten, insbesondere Angaben über seine Gesundheit, und Videoaufzeichnungen über mein Kind erhoben und in Papierform sowie auf elektronischen Datenträgern in der Kinderklinik der Heinrich-Heine-Universität Düsseldorf aufgezeichnet werden. Soweit erforderlich, dürfen die erhobenen Daten pseudonymisiert (verschlüsselt) weitergegeben werden:

a) an die Koordinierungsstelle für Klinische Studien der Universität Düsseldorf sowie zur wissenschaftlichen Auswertung in pseudonymisierter Form an das Auftragsforschungsinstitut M.A.R.C.O GmbH & Co KG, Düsseldorf

b) im Falle schwerwiegender unerwünschter Ereignisse: an die Ethikkommission der Heinrich-Heine-Universität Düsseldorf

2. Außerdem erkläre ich mich damit einverstanden, dass autorisierte und zur Verschwiegenheit verpflichtete Beauftragte des Auftraggebers in die beim Prüfarzt vorhandenen personenbezogenen Daten über mein Kind, insbesondere seine Gesundheitsdaten, Einsicht nehmen, soweit dies für die Überprüfung der ordnungsgemäßen Durchführung der Studie notwendig ist. Für diese Maßnahme entbinde ich den Prüfarzt von der ärztlichen Schweigepflicht.

3. Ich bin darüber aufgeklärt worden, dass ich jederzeit die Teilnahme meines Kindes an der klinischen Studie beenden kann. Beim Widerruf meiner Einwilligung, an der Studie teilzunehmen, habe ich das Recht, die Löschung aller der bis dahin gespeicherten personenbezogenen Daten zu verlangen.

4. Ich erkläre mich damit einverstanden, dass die Daten meines Kindes nach Beendigung oder Abbruch der Studie mindestens zehn Jahre aufbewahrt werden. Danach werden die personenbezogenen Daten meines Kindes gelöscht, soweit nicht gesetzliche, satzungsmäßige oder vertragliche Aufbewahrungsfristen entgegenstehen.

_____	_____
Ort, Datum	Unterschrift des Sorgeberechtigten
_____	_____
Ort, Datum	Unterschrift des Sorgeberechtigten
_____	_____
Ort, Datum	Unterschrift des aufklärenden Untersuchers

Dr. med. Viviane Klingmann
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Einwilligungserklärung

Teilnahme an

„Randomisierte, einfach dosierte cross-over Studie in zwei parallelen Gruppen zur Untersuchung der Akzeptanz, Schluckbarkeit und Schmackhaftigkeit von drei oralen Plazebo-Formulierungen bei kleinen Kindern“

Dein Name: …….

Dein Geburtsdatum: …….

Nachdem ich Dir die geplante Untersuchung mit Hilfe eines Comics erklärt habe, bist Du bereit daran teilzunehmen. **Aus den Dingen, die wir während der Untersuchung über Dich aufschreiben, wird niemand ablesen können, wie Du heißt und niemand, der nicht an dieser Untersuchung mitarbeitet, darf in Deine Krankenakte hineinschauen.**

Die Entscheidung zur Teilnahme an der Untersuchung hast Du freiwillig getroffen, nachdem Du verstanden hast, warum diese Studie gemacht wird, was Du in dieser Untersuchung erleben wirst und was vielleicht dabei passieren könnte. Jederzeit kannst Du Deine Teilnahme beenden. Dazu musst Du keine Gründe nennen und Du bekommst dadurch auch keine Nachteile. Dies gilt auch dann, wenn Du Deine Unterschrift zu dieser Einwilligungserklärung schon gegeben hast. Deine Eltern behalten eine Kopie der Teilnehmerinformation und Du kannst das Comic behalten. Wenn Du Fragen hast, kannst Du jederzeit auch Frau Dr. med. Viviane Klingmann ansprechen.

_____	_____
Ort, Datum	Unterschrift des Kindes
_____	_____
Ort, Datum	Unterschrift des aufklärenden Untersuchers

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6.5 Flyer

UKD Universitätsklinikum Düsseldorf

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

Wir werden Sie während Ihres ambulanten oder stationären Aufenthaltes persönlich ansprechen und aufklären. Für Fragen stehen wir jederzeit gerne zur Verfügung.

Ihre Ansprechpartnerin

Dr. med. Viviane Klingmann

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Funk 715 0480
Fax 0211-81 19512
viviane.klingmann@med.uni-duesseldorf.de

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„Studie zur Akzeptanz einer Oblongtablette im Vergleich zu Minitabletten und Sirup bei Kleinkindern“

Klinik für Allgemeine Pädiatrie,
Neonatologie und Kinderkardiologie

Sehr geehrte, liebe Eltern,

wie schaffen wir es, dass Kinder dringend benötigte Medikamente besser oder vielleicht sogar gerne einnehmen und schlucken? Wahrscheinlich kennen Sie die Probleme bei der Verabreichung von Arzneimitteln an Ihr Kind.

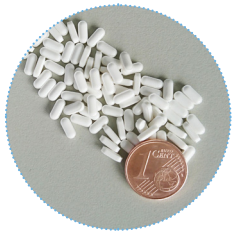
Wir haben bisher kaum wissenschaftlich zuverlässige Daten darüber, was am besten für Kleinkinder geeignet ist und welche Darreichungsformen einfach und sicher eingenommen werden: Tabletten, Sirup oder Ähnliches? Wir wissen aber, dass keine dieser Möglichkeiten für alle Kinder optimal ist. Hier in der Universitätsklinik Düsseldorf möchten wir versuchen, durch die Mithilfe Ihres Kindes, geeignete und altersgerechte Darreichungsformen für Medikamente für Kinder zu finden.

Die Schwierigkeiten

- Sirup: keine lange Haltbarkeit, keine zuverlässige Dosierung und Verabreichung, schlechter Geschmack, große Mengen
- Tabletten: kaum altersgerechte Größen und Dosierungen, schwer zu schlucken, Gefahr von Über- oder Unterdosierung durch Zerbrechen und Auflösen der Tabletten
- Minitabletten: von kleinen Kindern sehr gut akzeptiert, auch wenn mehrere Minitabletten auf einmal verabreicht werden, aber wir müssen noch Alternativen untersuchen

Eine mögliche Lösung

- Neu entwickelte Tabletten in kindgerechter Form und Größe, die mit einem Getränk heruntergeschluckt werden: genauere Dosierung, zuverlässiges Schlucken, geringeres Risiko für Verschlucken



Die klinische Studie

In dieser wissenschaftlichen Untersuchung soll erforscht werden, ob Kinder zwischen dem ersten und sechsten Geburtstag diese, speziell für Kinder entwickelte, längliche Tablette besser schlucken als bereits getestete und für kindgerecht befundene Minitabletten oder einen herkömmlichen Sirup. Welche Darreichungsform akzeptieren sie eher?

Die Testprodukte

- enthalten keine Medikamenten-Wirkstoffe (lediglich Plazebo)!
- 1 Oblongtablette (längliche Tablette: 6 x 2,5 mm) oder 3 Mini-Tabletten (2 x 2 mm) werden auf die Zunge gelegt und mit einem Getränk der Wahl verabreicht
- 3 ml Glucosesirup wird mit einer Pipette verabreicht

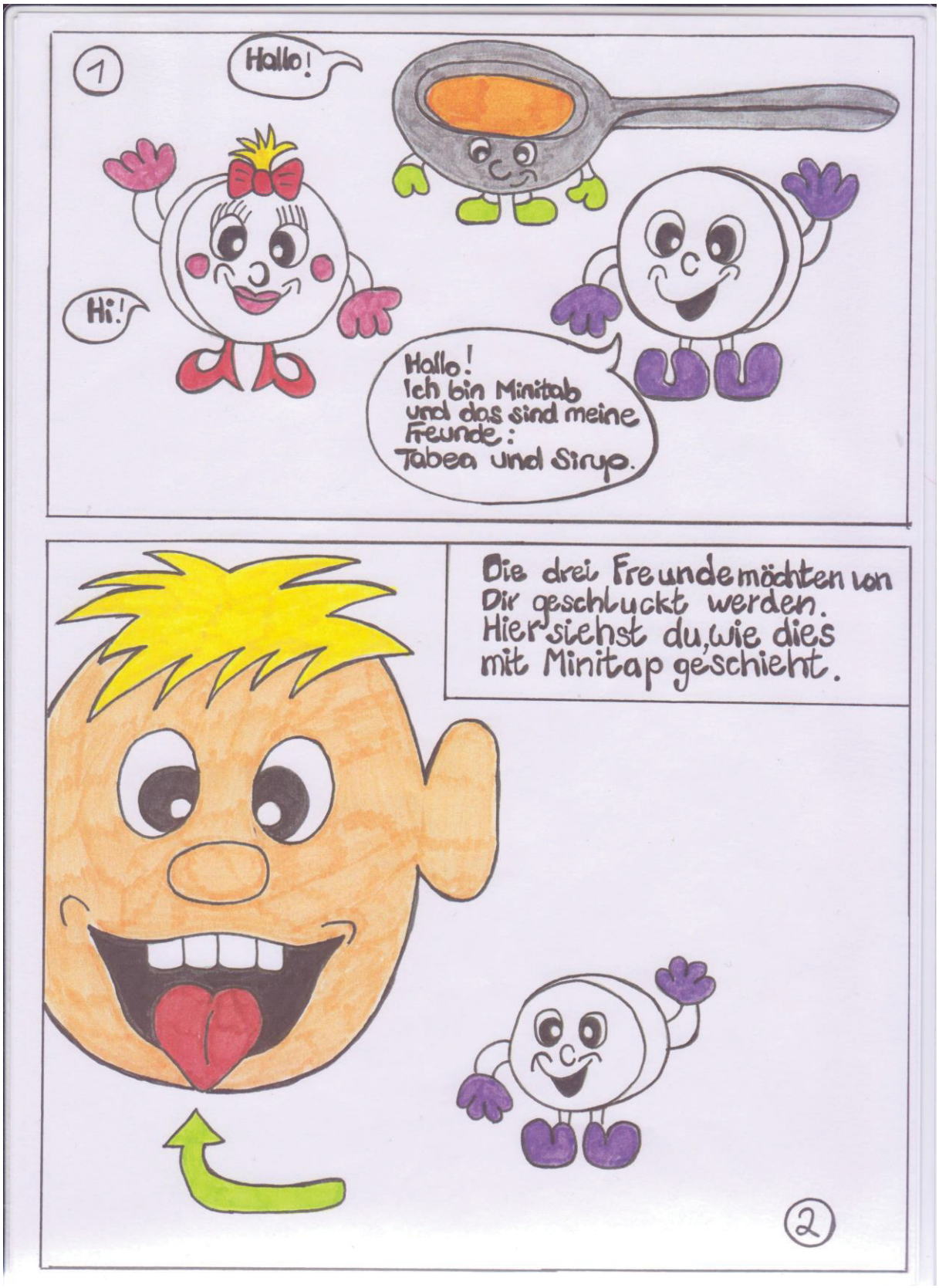
Ablauf der Untersuchung

- Einmalig zwei Schluckversuche innerhalb von 15 Minuten: Ihr Kind erhält entweder die Oblongtablette und die 3 Mini-Tabletten oder die Oblongtablette und den Sirup.
- Die Art und Reihenfolge der verabreichten Dosierungsformen ist zufällig
- Die beiden Schluckversuche werden auf Video aufgezeichnet und ausgewertet

Vorteile und Risiken

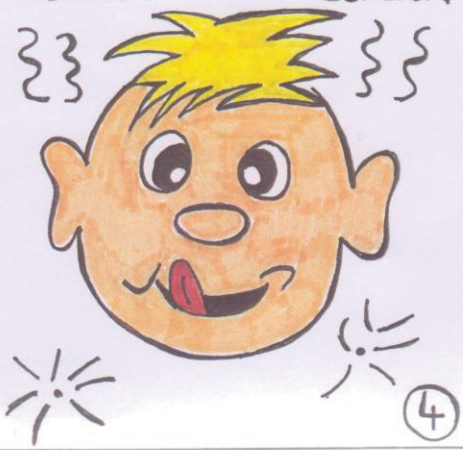
In einem persönlichen Gespräch werden Sie über die Vorteile und möglichen Risiken sowie den genauen Ablauf der Untersuchung ausführlich aufgeklärt. Ihr Kind hat keinen Vorteil von der Teilnahme an dieser Untersuchung, da ja kein Wirkstoff in den drei Darreichungsformen enthalten ist. Aber dafür birgt diese Untersuchung auch nur minimale Risiken und bedeutet nur eine sehr geringe Belastung für Ihr Kind. Sie helfen damit, dass wir für viele kranke Kinder in Zukunft klarer wissen, welche Darreichungsform zuverlässig und akzeptabel ist und damit die Medikamentenverabreichung deutlich vereinfachen können.

6.6 Comic


1
Hallo!
Hi!
Hallo!
Ich bin Minitab
und das sind meine
Freunde:
Tabea und Sirup.
Die drei Freunde möchten von
Dir geschluckt werden.
Hier siehst du, wie dies
mit Minitap geschieht.
2

Nun darfst du auch etwas Leckeres trinken

③

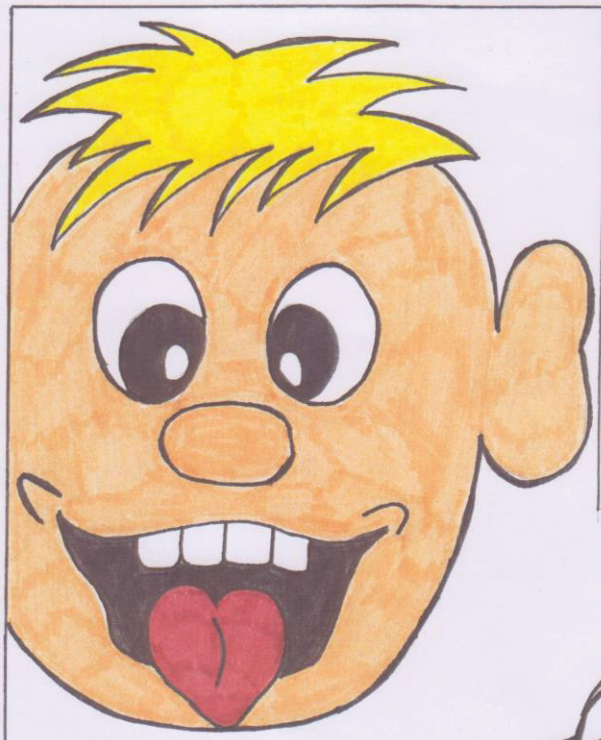


④

⑤

Wenn du das nicht möchtest, dann sag: „Nein!"


Hier siehst du, wie Sirup geschluckt wird. Danach darfst du aber nichts trinken.
6
Schluck
7
Schluck
Wenn du das nicht möchtest dann sag: „Nein!"
Nein
8



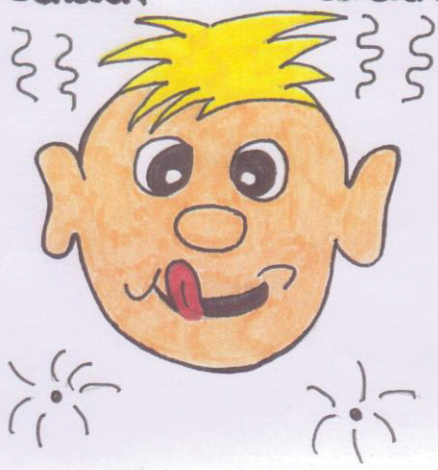
Nun siehst du, wie Tabea geschluckt wird. Danach darfst du wieder etwas von deinem leckeren Getränk trinken.

Die Reihenfolge in der du die drei Freunde bekommst, wird eine Überraschung

9

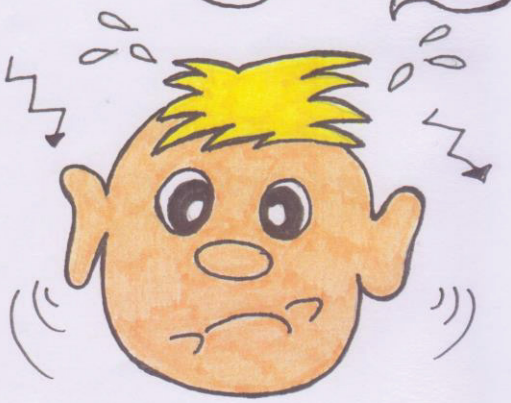
10

Schluck Schluck

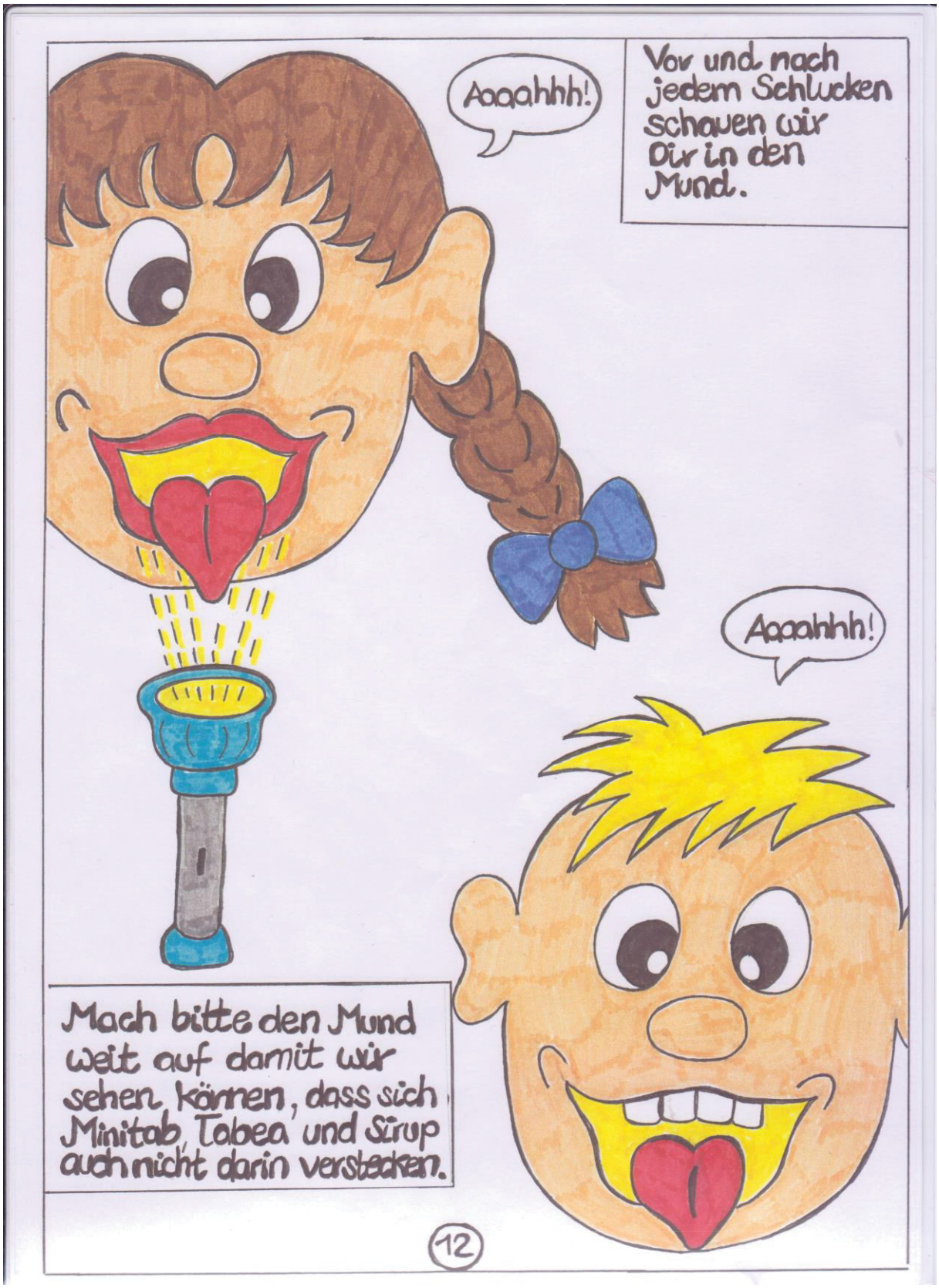


11

Nein



Wenn du das nicht möchtest, sag: „Nein!"


Aaaahhh!
Vor und nach jedem Schlucken schauen wir Dir in den Mund.
Aaaahhh!
Mach bitte den Mund weit auf damit wir sehen können, dass sich Minitab, Tabea und Sirup auch nicht darin verstecken.
12

13

Wenn du nicht mehr willst, dann sag: „Stop!"

DANKE

Tschüss!

dass du mitmachst!

14

Acknowledgement

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