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Investigation of the suitability of three oral dosage forms for small children of different age groups

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Favorable Acceptance of Mini-Tablets Compared with Syrup:

A Randomized Controlled Trial in Infants and Preschool Children

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Zusammenfassung

Das Fehlen von ausreichenden evidenzbasierten Therapieoptionen für Kinder verschiedener Altersgruppen führt zur Verabreichung von potentiell inadäquaten Substanzen und Dosierungen in der pädiatrischen Population.

Der aktuelle Goldstandard, den Kindern die Medikation in Form von Flüssigkeiten oder Sirups zu verabreichen, führt zu einer überraschend ungenauen Dosierung mit der Gefahr erheblicher Unter- oder Überdosierung. Daher ist es nicht nur notwendig, die Wirksamkeit und die optimale Dosis von pharmazeutischen Substanzen für die einzelnen pädiatrischen Altersgruppen zu untersuchen, sondern auch geeignete altersgerechte galenische Formulierungen für die optimale Verabreichung zu entwickeln und zu untersuchen.

Während die WHO den Gebrauch von festen Darreichungsformen in allen Altersgruppen empfiehlt, möchte die EMA Evidenz für die Eignung der festen Formulierungen in der jeweiligen Altersgruppe erhalten.

Bisher waren kaum wissenschaftliche Daten zur Anwendbarkeit und Schluckbarkeit von Minitabletten bei kleinen Kindern verfügbar. Das Ziel der beiden von der Autorin durchgeführten Studien an insgesamt 366 Kindern war es, valide Daten zur Akzeptanz von Minitabletten bei Kindern zwischen 6 Monaten und sechs Jahren zu generieren.

Über alle Altersgruppen gemittelt war die *Akzeptanz* (Geschluckt oder Gekaut/Geschluckt) der unbeschichteten Minitablette höher als die des Sirups (Differenz in Proportionen 14.8%, 95% KI 10.2-19.4; P <0.0001)). Auch in allen Untergruppen war die Akzeptanz der ungbeschichteten Minitablette der des Sirups überlegen oder zumindest vergleichbar. Einige Kinder zwischen 2 - 4 Jahren kauten die Minitabletten, dennoch ist die Akzeptanz als gut zu werten.

Die *Schluckbarkeit* der Minitabletten zeigte Unterschiede in den einzelnen Altersgruppen: gerade sehr junge Kindern waren vollständig in der Lage die Minitabletten ohne Kauen zu schlucken.

Überraschenderweise haben die kleinsten Kinder die Minitabletten besser akzeptiert als den Sirup. Dieses Ergebnis führte zu einer Änderung der Einschätzung der EMA bezüglich der Eignung von festen Darreichungsformen bei kleinen Kindern.

Insgesamt fand die Autorin heraus, dass bei kleinen Kindern sowohl die Akzeptanz, als auch die Schluckbarkeit von beschichteten und unbeschichteten Minitabletten der des Sirups überlegen sind.

Abstract

The lack of sufficient evidence-based therapeutic options for children leads to administration of potentially inadequate substances or dosages in the paediatric population.

The current gold standard - application of medicines in form of liquids or syrup – results in surprisingly inaccurate dosing with the danger of substantial under- or over-dosing. Therefore it is not only necessary to investigate the efficacy and the optimal dose of pharmaceutical substances for the different paediatric age groups but also to develop and investigate suitable age specific galenic formulations.

While WHO recommends the use of solid dosage forms in all age groups, EMA insists in receiving evidence for the suitability of solid dosage forms in the respective age groups.

So far only few scientific data on applicability and capability to swallow mini-tablets in small children had been available. The aim of the two performed studies in 366 children, presented by the author, was the generation of valid data on acceptability of mini-tablets in children between 6 months and 6 years.

The average *acceptability* (swallowed or swallowed/chewed) of the uncoated mini-tablet over all age groups was higher than that of the syrup (difference in proportions 14.8%, 95% CI 10.2-19.4; $P < .0001$). Also in all age subgroups acceptability of the uncoated mini-tablet was superior to that of the syrup or at least comparable. Some children between 2 and 4 years chewed on the mini-tablets but the acceptability was still rated to be good.

Differences in *capability to swallow* were detected in the different age groups: especially very young children were completely able to swallow the mini-tablets without chewing.

Surprisingly the smallest children accepted the mini-tablets better than the syrup. This result led to a change in EMA´s assessment concerning suitability of solid dosage forms for small children.

All together, the author found out that small children´s acceptability and capability to swallow of coated and uncoated mini-tablets were superior to the syrup.

List of Abbreviations

AMG	Arzneimittelgesetz
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
d	day(s)
DRKS	Deutsches Register Klinischer Studien
Ø	Diameter
e.g.	exempli gratia, for example
EMA	European Medicines Agency
et al.	et alia
EudraCT	European Union Drug Regulating Authorities Clinical Trials
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
i.e.	id est, this means
KKS	Koordinationszentrum für Klinische Studien
m	Month(s)
mm	Millimeter(s)
ml	Milliliter(s)
§	Paragraph
p	statistical power
PEI	Paul-Ehrlich-Institut
PIP	Paediatric Investigation Plan
PUMA	Paediatric Use Marketing Authorisation
UK	United Kingdom
WHO	World Health Organization
y	year(s)

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1. Introduction

1.1 Regulatory framework

Traditionally, the development of new pharmaceutical treatments has been performed for adult patients with the result that for only 10-50% of medicines administered to children researched-based data on appropriate drugs and doses are available (1,2,3,4). In all other cases drugs are used off-label which means that the medicines have not been tested on efficacy, safety or appropriate doses nor having gone through a marketing authorization process for this indication.

While parents are very much concerned about receiving suitable treatment for their sick children, pharmaceutical companies in most cases financing and organizing new drug development, have less commercial interest in development of paediatric treatments as children are generally prescribed fewer drugs for a shorter period than adults (5). The high development costs and limited expected gain of new paediatric drugs pose a major disincentive for the pharmaceutical industry. Additionally, the limited number of eligible trial subject yields its own practical problems such as inadequately powered studies and inability to demonstrate moderate but clinically relevant treatment effects (6). This problem is expanded by the heterogeneity of the paediatric population and thus the requirement of stratification according to age groups. Furthermore, recruitment is difficult in paediatric research (7,8) due to the limited number of children with specific diseases, fear or inconvenience of parents to let their child participate and the need for narrow in- and exclusion criteria to keep variability low in those studies with low subject numbers. In addition, the fact that few paediatric treatments have marketing authorization the choice of comparators in clinical trials creates a major problem when designing a paediatric development plan.

The complexity of paediatric trial performance is further increased by a number of ethical requirements:

- additional toxicity studies and sufficient data from adult studies should be available before a new pharmaceutical product is administered to children
- the study concept must ensure minimal risk and minimal burden while balanced against associated benefits of trial participation
- the paediatric development should start with trials in older children to protect the even more vulnerable population of small children, thus often requiring several studies
- in most European countries informed consent needs to be received from both parents
- the additional request for receiving assent from the children poses additional complexity to the preparation and conduct of the clinical trial
- placebo control is even more restricted than in adults

- inclusion of healthy children in a clinical trial is in principle forbidden or considered ethically unacceptable (9).

All these ethical considerations have been extensively debated and described in worldwide accepted documents such as “The Declaration of Helsinki” (10), the “ICH Topic E11”-guideline (11) and the EMA´s guideline “Ethical considerations for clinical trials on medicinal products conducted with the paediatric population” (12) which formed the ethical basis for the requirements on paediatric development laid down in the “Paediatric Regulation” (Regulation (EC) No 1901/2006 of the European Parliament and of the Council) (13) having come into force in 2006 as binding law in all European member states.

The main objectives of this Regulation are to:

- increase awareness for the need of clinical research in the paediatric population
- improve the health situation of the paediatric population
- improve and strengthen the quality of the research and consideration of the ethical standards in the field of paediatric medicinal products
- improve the availability of authorised paediatric medicinal products
- decrease/prevent non-essential clinical trials with children.

It is the aim of the Regulation to encourage pharmaceutical companies to develop better medicines for children without delaying the marketing authorization of new medicines for adult indications. To make sure that paediatric development becomes a part of the overall medicinal product development, the Regulation introduced the need for approval of a Paediatric Investigation Plan (PIP) at the end of early clinical development and execution of this plan before submission of the Marketing Authorization Dossier. This difficult and costly obligation, however, is counterbalanced by incentives for the pharmaceutical industry such as extension of the patent for six months, extension of the protection period to 12 years for orphan medicinal products, pursuant to the “Orphan Drug Regulation” (Regulation (EC) No 141/2000 (14)), and the “Paediatric Use Marketing Authorisation” (PUMA) (13) providing a 10 years data and marketing protection period for the development of paediatric indications for drugs off patent.

While the “Paediatric Regulation” created the marketing frame for paediatric development in Europe, the European “Clinical Trials Directive” (Directive 2001/20/EC) (15) defines the conditions for performing clinical trials according to Good Clinical Practice (GCP) (16) also in the paediatric population in Europe. The principles of this “Clinical Trials Directive” were introduced into the German legislation by the 12th amendment to the German “Arzneimittelgesetz” (AMG) (17) and the “GCP-Verordnung” (18). The German drug law requires the approval of the clinical trial dossier by the competent authority (“Bundesinstitut für Arzneimittel und Medizinprodukte” (BfArM) or the

“Paul-Ehrlich-Institut” (PEI) for biologicals and blood products and a favorable opinion from the relevant Ethics Committee before a clinical trial with a medicinal product can be started. Clinical trials that do not fall into the scope of the AMG only need a favorable opinion from the Ethics Committee according to the German Physicians’ Law which requires that every physician intending to perform research in humans must seek ethical and legal advice from the ethics committee responsible for him/her (19).

With the implementation of the “Clinical Trials Directive” a European register for clinical trials with medicinal products (European Union Drug Regulating Authorities Clinical Trials (EudraCT)) was established at the European Medicines Agency (EMA) in London, UK, to achieve an overview for competent authorities over all clinical trials with medicinal products performed in Europe. Registration in such a register is not a legal obligation for all other types of clinical trials. However, to avoid publication bias the “International Committee of Medical Journal Editors (ICMJE)” made the registration of the clinical trial in a publicly accessible register a precondition for publication of the study results in their journals. The German “Deutsches Register Klinischer Studien (DRKS)” is such an internationally accepted register and widely used by German clinical researchers.

In conclusion, it can be stated that the high medical need, the nowadays also in Germany fully implemented regulatory framework for paediatric medicines development and the well-established ethical conditions for clinical research in children form an attractive basis for pharmaceutical companies and academic researchers to work on better medicines for children taking into consideration their different physiological conditions and their particular need for drug administration.

1.2 Children´s physiology

Differences between Children and Adults

Children can neither be regarded as small adults nor as a homogeneous group in themselves. The one constant in childhood development is change. Pharmacokinetics and pharmacodynamics differ as compared to adults with huge implications on the development and use of medicines for children (20, 21). “With age, large changes in total body water, body water distribution and body composition occur. Infants have a much larger proportion of body weight in the form of water than do adults. The foetus has high total body water that at birth accounts for approximately 75% of the body weight in the full-term new-born infant and 80% in the preterm new-born. The total water decreases during the first year of life to approximately 60% of body weight and stays at that level until puberty. In addition, the distribution of body water is also different. In term infants, 45% and 35% of body water is extracellular and intracellular respectively, whereas in adults, it is 20% and 40% respectively.”

While the total body water decreases with age the muscle and fat content as well as protein binding increase (21).

When a child is born, liver and renal functions are not yet totally developed: hepatic blood flow as well as liver enzyme composition and activity increase with age of the child. “Along with changes in hepatic maturation developmental changes occur with the renal function. Both anatomical and functional immaturity of renal tubules is present at birth, and both, passive reabsorption and active secretion are diminished. … Developmental changes in renal function can dramatically alter the plasma clearance of compounds with extensive renal elimination and thereby affect the age-appropriate selection of a dosage regimen.” [Peter J. Davis (2006) (21)]

Rate and extent of bioavailability are also significantly impacted by the developmental changes in the gastrointestinal tract and skin: gastric pH is relatively high in the neonatal period; gastric emptying increases; gut motility matures during early infancy and there are changes to splanchnic blood flow, intestinal drug metabolising enzymes, micro flora and transporters (22).

“In addition to kinetics, differences in drug transporter proteins as well as drug receptors occur. These changes lead to variability of the drug response.” [Peter J. Davis (2006) (21)]

Also the blood-brain barrier is not fully mature at birth but little information is available about its maturation process. With increasing age children achieve several important milestones of psychomotor development with improvement of cognitive and motor skills (11).

The deglutition process of small children is not yet well investigated. Only little information is available on development and timing of the maturation of the deglutition process. Paediatric experience, however, shows that children as of six months are able to swallow solid particles in their meal. According to the investigations of Ruark JL et al. (23) at the latest at the age of five years children employ adult-like control strategies during swallowing: “significant differences in duration and magnitude of muscle activity resulted as a function of bolus consistency. General observations revealed, however, that swallowing in children is characterized by muscle activity that is shorter in duration.”

Until the complete maturity of the organs the dosage of medications has to be adapted. These developmental changes affect differences in drug administration, disposition, metabolisation and excretion and therefore adaptation of drug dosage and administration of the drug through adequate galenic formulation become necessary.

1.3 Classification in age ranges

To ensure optimal efficacy and safety of an administered drug it is important to identify the optimal dose and route of administration for the respective development stage of the child. Different approaches to a definition of suitable age ranges have taken place:
while the WHO distinguishes only between three age groups

- Neonate: 0–28 days
- Infant 1–12 months
- Child 1–12 years

and the International Conference on Harmonisation (ICH) E11 Guideline on "Clinical Investigation of Medicinal Products in the Paediatric Population" (11) defines five categories

- Preterm new-born infants
- Term new-born infants: 0-27 days
- Infants and toddlers: 1-23 months
- Children: 2-11 years
- Adolescents: 12-16 or 18 years

the European Medicines Agency (EMA) splits ICH´s category 4 (children 2-11 years) into two categories and arrives at the following six different paediatric populations with regard to their age-specific characteristics and standard biological changes (22).

- Preterm new-born infants
- Term new-born infants: 0-28 days
- Infants and toddlers: 1 month - 2 years
- Children (pre-school): 2-5 years
- Children (school): 6-11 years
- Adolescents: 12-16 or 18 years

In the investigation of new paediatric galenic formulations even the EMA´s six categories might not be specific enough, especially until the age of six years, because major changes in the development of all body systems occur in the first years of life.

1.4 Development of paediatric galenic formulations

Currently, small children receive their orally applied medication mostly in form of oral solution or syrup due to lack of knowledge about the ability of small children to swallow solid particles. However, application of solutions is unreliable as children let small runlets flow out of the mouth, spit it out and/or there remain leftovers on the spoon. This results in a surprisingly unreliable

dosing with substantial under- or over-dosage (24). 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 age-adapted galenic formulations for the most suitable routes of administration. Currently, the most important problems of oral formulations exist in the lack of availability of the individually required dose, total volume and the small child's inability to ingest standard-size solid dosage formulations, and the unpleasant taste of some liquids. This sometimes results in a choice of an alternative formulation, e.g. 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 (22) and little scientifically sound data are available on suitability of different formulations in children of different age groups. 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 (22).

Krause and Breitkreutz (25) 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.

In 2006 the EMA released the "Reflection Paper: Formulations of Choice for the Paediatric Population" (22) providing a summary of the current stage of knowledge on paediatric formulations. They 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. 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 (Table 1: extract concerning peroral forms).

Matrix: Route of administration/ oral dosage form vs. age (22)

Route Dosage Form	*Preterm new-born infants*	*Term new-born infants (0d-28d)*	*Infants and Toddlers (1m-2y)*	*Children (preschool) (2-5y)*	*Children (school) (6-11y)*	*Adolescents (12-16/18y)*
Peroral						
Solution/Drops	2	4	5	5	4	4
Emulsion/ Suspension	2	3	4	5	4	4
Effervescent Dosage Forms	2	4	5	5	4	4
Powders/ Multi-particulates	1	2	2	4	4	5
Tablets	1	1	1	3	4	5
Capsules	1	1	1	2	4	5
Oro-dispersable Dosage Forms	1	2	3	4	5	5
Chewable tablets	1	1	1	3	5	5

Table 1:

For the early ages the code indicates mainly the applicability of the route and the dosage form:
1 not applicable
2 applicable with problems
3 probably applicable, but not preferred
4 good applicability
5 best and preferred applicability,

For the higher ages more or less all dosage forms might be principally applicable, but with increasing age the preference of the children becomes more important:

1 not accepted
2 accepted under reserve
3 acceptable
4 preferred acceptability
5 dosage form of choice

From the left to the right columns in the table, the focus shifts from the applicability to the preference.

In 2008 the World Health Organization´s (WHO) recommendation was the use of solid multiparticulates in children: “there was general acceptance of the benefits of solid dosage forms over liquid dosage forms for stability, dosing and administration issues.” (26)

In 2011 the EMA released the draft “Guideline on Pharmaceutical Development of Medicines for Paediatric Use” (27) where it was stated that “oral liquid dosage forms are normally considered acceptable for children from full term birth” and “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 of 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.”

The consensus process for this draft guideline has resulted in numerous comments for improvement including information on our own research results on coated and uncoated mini-tablets. A second version of the EMA draft guideline has been published for comments in January 2013. In this version the EMA does not give anymore any age range recommendation for the suitability of solid oral dosage forms. Also the mini-tablet approach was assessed more favourably than in the first draft guideline (28). After a second consensus process the final version of the guideline (29) was published in August 2013 and will come into effect in February 2014. The content of the chapter on solid dosage forms (including mini-tablets) was not changed anymore.

1.5 The mini-tablet strategy

Obviously, there is great need for a safe, reliable and acceptable oral paediatric formulation for small children and scientifically sound data from a comparison between different oral paediatric administration routes concerning suitability and capability to swallow of children, particularly in young age, to identify the most suitable form of galenic formulation for the respective age group.

In paediatric practice syrup is so far the most frequently used formulation. But solid dosage forms have strong advantages over liquids: they are easy in handling, reliable in content uniformity and drug administration, safer concerning excipients and cheaper in production. Moreover, they provide advantages over liquid formulations regarding drug stability, storage conditions (26) and precision of dosing. However, usual sized tablets may cause swallowing and compliance problems especially for small children and the dose might not be age adapted. Current general paediatric practice includes crashing and dissolving of tablets for adults. This does not allow reliable dosing and reduces children´s acceptability to swallow medicine, often due to bad taste. Therefore attempts had to be made to develop smaller age adapted solid dosage forms, e.g., mini-tablets. Experience with mini-tablet technology (direct compression tabletting) exists from substances difficult to press into

tablet form like Pankreatin, Valproinacid and Omeprazol, where mini-tablets are filled into capsules or sachets.

Mini-tablets are solid dosage forms with a diameter of maximum 3.0mm (30). They also exist in coated form, for taste-masking or slow substance release purposes. Usually considered as multi-particulate formulations they are administered with different types of devices, e.g., dosing spoons. Applying the mini-tablet technology for children requires exact provision of the required number of mini-tablets. Different mechanical and electronic mini-tablet delivery systems that allow a flexible choice of mini-tablets have been developed or are currently under development (31, 32, 33).

To fulfil the specific needs for reliable and acceptable administration of different active substances to small children two different types of mini-tablets were developed: coated and uncoated mini-tablets (Figure 1):

Dimensions of mini-tablets

Fig.1: Uncoated (left) and coated mini-tablets (right) in relation to a 1 Euro cent coin (centre)

Uncoated mini-tablets disintegrate after several seconds when in contact with saliva. The risk of choking on these mini-tablets is therefore very low and thus considered to be a particularly good way to administer medicine to young children. However, disintegration and drug dissolution may affect compliance when drug molecules with unpleasant taste are administered.

The coated mini-tablets do not dissolve in the mouth. Their advantages are the possibility for taste masking (34), for hiding excipients or active substances potentially irritating the oral mucosa with an adequate coating material, and the avoidance of starting digestion by the gastric acid by only dissolving after stomach passage. Polymer coating may also be used to enable sustained-release characteristics.

The ingredients of the two forms of mini-tablets were as follows:

A) Uncoated mini-tablet ø 2mm, total weight: 7,846mg/unit

- Lactose
- Cellulose
- Magnesium stearate
- Anhydrous colloidal silicon dioxide

Manufactured at Institut für Pharmazeutische Technologie und Biopharmazie, Heinrich-Heine Universität Düsseldorf

B) Coated mini-tablet ø 2mm, total weight: 9,246mg/unit

- Lactose
- Cellulose
- Magnesium stearate
- Anhydrous colloidal silicon dioxide
- Coating: - Pharmacoat 606 (Hypromellose)
  - Macrogol 1500

Manufactured at Institut für Pharmazeutische Technologie und Biopharmazie, Heinrich-Heine Universität Düsseldorf.

1.6 Manufacturing of glucose syrup

The ingredients of the 15% glucose syrup (total weight: 287,5g) were as follows:

- Glucose-Sirup GÄ 40%, Fagron 250,0g
- Water 37,5g

Manufactured at Klinik für Allgemeine Pädiatrie, Neonatologie und Kinderkardiologie of the Heinrich-Heine-Universität Düsseldorf or at the Central Pharmacy of the University Hospital Düsseldorf.

1.7 Previous research by other authors

In 2009 Thomson et al. (34) published the results from an open, prospective uncontrolled, single-dose study in 100 children aged 2 to 6 years, divided into 4 subgroups (2-3, 3-4, 4-5 and 5-6 years) with administration of one 3 mm diameter drug-free uncoated mini-tablet. In this study only 46% of the 2-year-lold children were able to swallow the mini-tablets, whereas up to 86% of the oldest children were capable of swallowing these mini-tablets. The authors therefore concluded that it was safe to use 3-mm mini-tablets in children aged 4–6 years.

The value of these results is limited as

- the study was uncontrolled,
- the sample size was not statistically powered,
- no information on the suitability for children below 2 years was provided,
- the result of the swallowing act was not actively controlled and
- the size of the mini-tablet was relatively large with a diameter of 3 mm.

In 2011, Van de Vijver et al. (35) published the result of a prospective, randomized study in 16 children, aged 6 to 30 months, with cystic fibrosis, administering 4 different doses of Pancrelipase via 1 to 4 enteric coated, 2 mm diameter mini-tablets over 5 days. The primary endpoint was the effect of pancrelipase, palatability of the mini-tablets as a secondary parameter. “Palatability was scored fair to good by the parents in each of the treatment groups.”

In 2013, van Riet-Nales et al. (36) published the results of a prospective, randomized, cross-over study in 148 children, aged 1 to 4 years, with the aim to investigate the acceptability of and the preference among four oral placebo formulations (small (4mm) tablet, powder, suspension and syrup) in domiciliary infants and preschool children. Parents were asked to report the child´s acceptability by a score on a 10cm visual analogue scale (VAS) and by the result of the intake. At the end of the study they were asked to report the preference of the child and of themselves. Results showed that the estimate of the mean VAS score was significantly higher for the tablet than for the suspension. The estimate of the mean number of intakes fully swallowed was significantly higher for the tablet than for the other formulations. Children and parents preferred the tablet and the syrup over the suspension and the suspension over the powder.

No other studies comparing different oral paediatric formulations including mini-tablets have been published.

1.8 Previous research by the author

With the exception of some pre-work from Thomson et al. there was no methodology described in literature to reliably measure the acceptability and capability to swallow solid oral formulations in children of different age-groups and the variability of such measurements.

In an open, randomised, two-way cross-over pilot study (37), performed by the author and collaborators at the Paediatric Clinic of the University Hospital of Düsseldorf in 2010, with 60 outpatient and inhouse patients, aged 6 months to 5 years inclusive, an uncoated, drug-free, 2 mm diameter mini-tablet was compared with 3 ml glucose syrup. The process of deglutition was carefully

observed and the result of swallowing assessed by oral inspection. The following evaluation criteria were assessed:

Mini-tablet:

- 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 a part of the solid, broken into minimum two pieces, was 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 was swallowed
    - which means that no liquid was left in the mouth and no drops left the mouth
    - interpreted as accepted and swallowed
- Small runlet was flowing out of the mouth
    - 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
- Choked 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 pipette or the teaspoon 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

The measurement method proved to be suitable to distinguish between the effects of the two different treatments and with 10 children in each of the six age groups sufficient data were provided to calculate the sample size of the following confirmatory study. It gave first hints that the acceptability ("swallowed" and "chewed") of the uncoated mini-tablet was superior to the syrup in most of the investigated age groups.

1.9 The study of this thesis

Aim of the present study was to confirm the results of the above described exploratory study and to further investigate whether coated and uncoated mini-tablets differ from syrup in acceptability and capability to swallow of small children. The study was a confirmatory, prospective, open, randomized, three-way cross-over, controlled study with 306 children aged 0.5 to 5 years inclusive. Preparation, performance and evaluation of this study is the subject of this thesis and described in the attached publication.

To ensure state-of-the art quality performance the study was designed and organized to fulfill all GCP-requirements:

- the design and study procedures respected all ethical requirements of the Declaration of Helsinki (10)
- the requirements of the ICH E6 guideline (16) (GCP guideline) were strictly followed, especially concerning responsibilities, qualifications of study staff, training, protocol, study management, data collection and management, statistical planning and evaluation, study documentation, reporting and filing
- a positive opinion from the "Ethikkommission der Heinrich-Heine-Universität Düsseldorf" was received (Number 3395)
- the study was registered in the "Deutsches Register Klinischer Studien" (Number: DRKS00000432)
- patient liability insurance was covered by the Zurich Versicherung (Nr. 800.540.008.368)
- monitoring was performed by the „Koordinierungszentrum für Klinische Studien" of the university (KKS Düsseldorf)
- written informed consent from both parents was achieved before inclusion of the patients into the trial and assent of the children was sought as far as possible

The study was an “investigator-initiated” trial as it was completely financed by the Heinrich-Heine Universität Düsseldorf without any sponsoring support from pharmaceutical industry.

1.10 Rationale for the study and study design (benefit-risk-ratio/ “minimal risk and minimal burden”, methodology)

Due to the lack of scientifically sound data on the suitability of oral formulations for children of different age groups and the experiences with dosing and stability problems with liquid formulations it was important to perform a physiological examination in a sufficiently large number of patients of the particularly vulnerable age groups, namely 0.5 to 5 years, comparing coated and uncoated oral mini-tablets with the current standard, the syrup.
A three-way cross-over design was chosen in this study allowing intra-individual comparison of the children’s reaction to the ingestion of the three formulations as well as the reduction of the variability of data and thus the number of children required in this study. The comparison of three different formulations was possible because the cross-over pilot examination in 60 children performed with 2 different oral formulations had shown that repeated administration of oral formulations was acceptable for children of all age groups investigated. Randomisation of the three applications was chosen to avoid period and sequence effects.

In the pilot study “swallowed”, “chewed”, “spat out” and “refused to take” had proven to be suitable parameters to objectively assess the suitability of oral formulations for children for the different age groups. Therefore the same evaluation criteria were chosen for this physiological examination. The evaluation results were presented as “acceptability”, defined as the combination of the evaluation criteria “swallowed” and “chewed”, and as “capability to swallow” defined as “swallowed without chewing”.

The fifth evaluation criterion - “choked on” - was maintained in this physiological evaluation as well as the main safety concern expressed in the EMA draft guideline was the danger for especially young children to inhale particles or to cough after ingestion of solid oral dosage forms due to their lack of maturity of the deglutition act.

As no active drug substance was administered, blinding was not necessary to avoid observation bias and would have technically not been feasible.

2. Study Objectives

2.1 Objectives

The primary objective was: proof of superiority of the uncoated mini-tablet's acceptability over that of the syrup in the group of children between 0.5 and 5 years inclusive.

Secondary objectives were:

- Proof of children's ability to swallow a solid formulation as well as a liquid.
- Investigation of differences in the acceptability of the uncoated mini-tablet versus the syrup in each age group.
- Investigation of differences in the acceptability of the coated mini-tablet versus the uncoated mini-tablet, respectively the coated mini-tablet versus the syrup in each age group as well as for the whole population.
- Investigation of differences in the capability to swallow three different oral placebo formulations in each age group as well as in the whole population.
- Identification of differences in percentage of children in the different age groups who choked on any of the three oral placebo formulations.
- Identification of number of children who refused to take an oral placebo formulation or who spat it out.
- Identification of possible safety problems occurring during deglutition.
- Demonstration of children's ability to swallow a solid oral formulation beginning at the age of six months.
- Analysis of the compliance of children requested to swallow a mini-tablet or glucose-syrup.
- Identification of differences in palatability of the three oral placebo formulations.

2.2. Collaboration

The author's thesis was enabled by a collaboration between three different departments of the Heinrich-Heine Universität: the "Institut für pharmazeutische Technologie und Biopharmazie" , the "Klinik für Allgemeine Pädiatrie, Neonatologie und Kinderkardiologie", the "Koordinierungszentrum für Klinische Studien (KKS)" as well as a representative of the Cochrane Metabolic and Endocrine Disorder Group.

3. Publication

Publikation:

Favorable Acceptance of Mini-Tablets Compared with Syrup:

A Randomized Controlled Trial in Infants and Preschool Children

Viviane Klingmann, Natalie Spomer, Christian Lerch, Ines Stoltenberg, Cornelia Frömke, Hans Martin Bosse, Jörg Breitkreutz, Thomas Meissner

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4. Discussion

In addition to the points discussed in the publication a number of aspects of this research project need further considerations and description:

Developing age-adapted galenic formulations for children as requested by the EU Paediatric Regulation does not only require state-of-the art pharmaceutical development but also clinical testing in different age groups within a suitably designed clinical trial and within the national legal framework. The design, planning and rapid execution of such a large investigator-initiated study requires the availability of a strong collaboration between different university departments. In this study the collaboration between the University-owned “Institut für Pharmazeutische Technologie und Biopharmazie” and the “Klinik für Allgemeine Pädiatrie, Neonatologie und Kinderkardiologie” at the University Hospital Düsseldorf, supported by the University Hospital’s clinical trials coordination center (KKS), enabled this academia-initiated investigation of two newly developed mini-tablet formulations in comparison to the previously postulated “gold standard” syrup in a sufficiently large number of paediatric patients in a short period of time. Study objectives, endpoints, design, evaluation criteria and study procedures as presented in the study protocol (Attachment 7.1) and as approved by the Ethics Committee of the University (Attachment 7.2) were agreed by all parties involved. The study medication as well as the liability insurance for the study participants were provided by Prof. Dr. Jörg Breitkreutz, Institut für Pharmazeutische Technologie und Biopharmazie. The Principal Investigator with responsibility for study organisation and all medical aspects was PD Dr. Thomas Meissner, Klinik für Allgemeine Pädiatrie, Neonatologie und Kinderkardiologie. The GCP-certified (Attachment 7.3) investigators responsible for preparation, coordination, and execution of the study were the author of this thesis and Natalie Spomer. GCP compliance was ensured by the KKS by providing monitoring and Trial Master File support. KKS also provided the paper-based case report form and the database. Sample size calculation, randomization list, statistical evaluation, tables and graphs were provided by Dr. Christian Lerch, Cochrane Metabolic and Endocrine Disorders Group. The author of this thesis, PD Dr. Thomas Meissner, Prof. Dr. Jörg Breitkreutz, Dr. Christian Lerch and Natalie Spomer prepared the first draft of the publication and were supported by Dr. Hans Martin Bosse, Klinik für Allgemeine Pädiatrie, Neonatologie und Kinderkardiologie. All parties involved contributed to data interpretation, reviewed the draft, and approved the final version of the publication.

The patients of this study were recruited from three wards and three ambulances of the Klinik für Allgemeine Pädiatrie, Neonatologie und Kinderkardiologie of the Heinrich-Heine-Universität Düsseldorf. As requested in the protocol, 51 children per age group were recruited and assigned to the treatment order according to the randomization scheme. As presented in

Figure 2 in total 572 parents were approached for enrolment of their child. 266 children (46.5%) could not be included either because the parents refused inclusion of their child into the study, or because the medical history revealed that the patients fulfilled exclusion criteria, or because the patients were discharged from the hospital before they could be enrolled into the study.

Flow Diagram of Patient Distribution

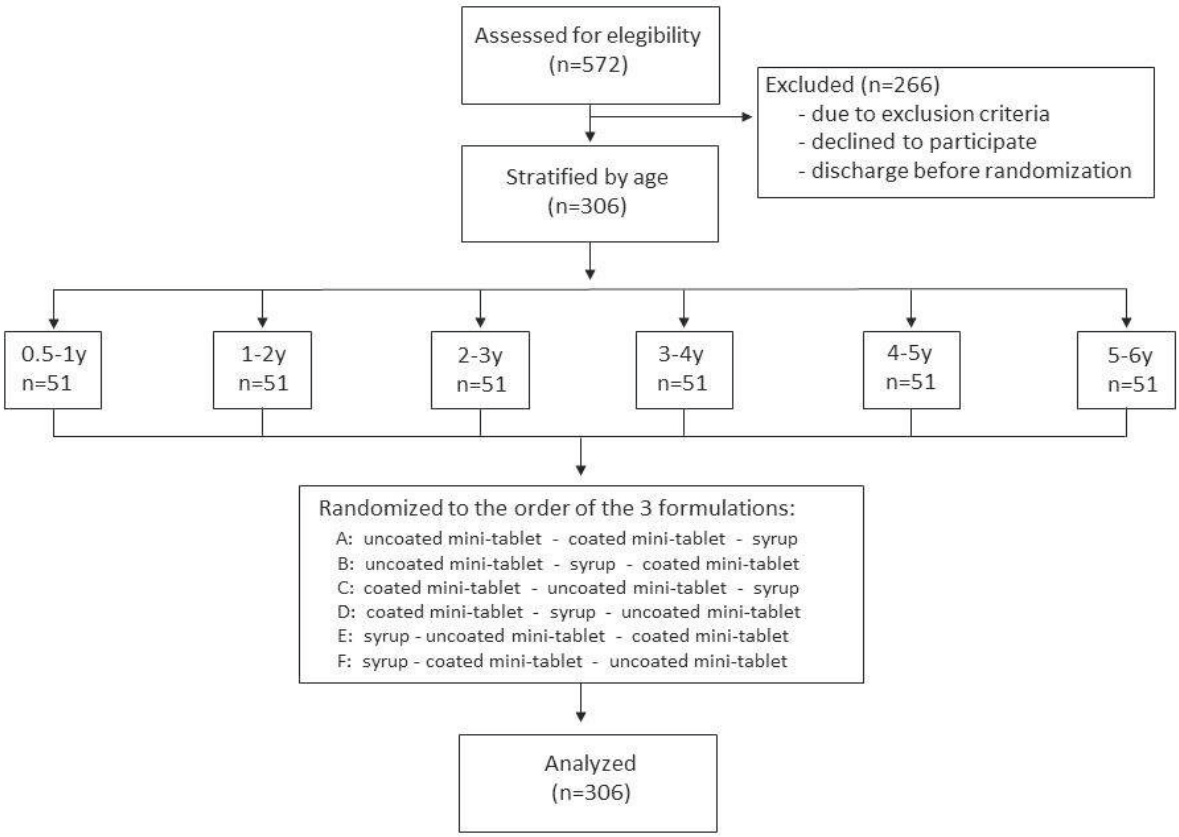

Fig.2: Overview of patients enroled

Before any study activity was performed both parents were informed about the study, its objectives, risks, benefits, and procedures in form of a patient information sheet (Attachment 7.4) and verbally by one of the investigators. They had sufficient time to ask questions and to consider the participation of their child before signing the informed consent form (Attachment 7.5). In case the child had only one parent or legal guardian informed consent was received from this person. As far as possible the study was explained to the child verbally by one of the investigators as well as in form of a comic (Attachment 7.6.) and assent (Attachment 7.7) was sought in writing if the child was able to do so.

One of the key activities of the „Institut für Pharmazeutische Technologie und Biopharmazie“ at the University of Düsseldorf is the development of solid oral drug formulations for children in an attempt to find alternatives to the “gold

standard" syrup and oral solutions. Syrup and oral solutions, also produced from crushed tablets, do not allow precise dosing by parents and care takers (24), children may not like the taste and therefore swallow only an uncontrolled amount of the applied dose, the stability is limited in hot climate, and the reconstitution of dry powder is unreliable and may be difficult if no clean water is available, especially in third world countries. Transport and storage are difficult and expensive due to the large volume. The calculation of the required dose and related volume based on the child's bodyweight in kg is quite complex and is a source of dosing errors. In contrast, solid oral dosage forms can be easily transported and stored, are less sensitive to climate conditions, can be reliably and easily applied but size may cause a problem, preferably in small children. Therefore, mini-tablets, preferably of a size of 2 mm diameter, are a viable option for all age groups. They allow the administration of a relatively large amount of active substance. However, dosing flexibility according to body weight is limited in solid oral dosage forms by the defined maximal amount of substance [2.5 mg] per 2mm diameter tablet. Thus they are more suitable for active substances with high pharmacological power. High doses require the administration of several mini-tablets which could reduce their acceptability, especially in severely sick children.

After successful completion of the pharmaceutical development of a new paediatric galenic formulation the clinical development needs to ensure that it is suitable for children. Its acceptability and reliability of administration need to be demonstrated in suitably designed and performed clinical trials, especially in those age groups that might have problems of ingestion. Due to the fact that the maturation process in small children is relatively unknown it is important to investigate the acceptability and capability to swallow in children between 6 months and 6 years, leaving out the most vulnerable population of newborns up to an age of 6 months. Testing in those very small children should be foreseen for a separate study once suitability for 6 – 12 months old children could be demonstrated. To reduce the risk of severely sick patients of receiving a treatment that is not efficacious it is necessary to first test the general suitability of the new galenic formulation in less severely sick patients that are in a condition to participate in a deglutition test with placebo administration. In case of the presented study this approach allowed the enrolment of a large number of study participants within a short period of time: 306 children were enrolled in 4.5 months in a single study centre.

While planning, performance, evaluation and reporting of this clinical trial had to follow the ethical standards of the Declaration of Helsinki and the quality standard of ICH-GCP, this clinical trial with only placebo-containing galenic formulations did not fall under the German "Arzneimittelgesetz" (17) as "§ 4 Abs.23 Satz 1" defines that only clinical trials containing any medicinal product fall under the legal obligations of the AMG. Placebo medication, however, is not an active medicinal product according to the AMG's definition. Therefore

the planned clinical trial did not need Clinical Trial Authorisation by the competent authority BfArM but only a favourable opinion from the university hospital's independent ethics committee according to the German physicians law. According to the BfArM's opinion this also meant that § 40 to 42 of the AMG did not apply and therefore it would have been justified - for German legal reasons – to include healthy children in this placebo investigation. However, German ethics committees communicate that they have informally agreed within their "Arbeitskreis medizinischer Ethikkommissionen in der Bundesrepublik Deutschland e. V." that clinical trials in *healthy children* – with exception of vaccine trials – are not considered to be ethically acceptable. There is no written statement of this agreement publicly available. As the planned study clearly followed the methodology of a clinical trial the inclusion of *sick children* needed to be enabled. Ethical requirements also demanded a positive benefit-risk ratio with minimal risk and minimal burden for the children enrolled. The Declaration of Helsinki, § 17, (10) considers medical research in vulnerable populations justified "if the research is responsive to the health needs and priorities of this population… and if there is a responsible likelihood that this population… stands to benefit from the results of the research". The administration of two single mini-tablets and 3 ml glucose-containing syrup without active ingredients was supposed to be performed in a child-friendly setting without invasive investigations but just a mouth inspection and thus did present only minimal burden to the children. The risk of coughing after administration of the formulations could be expected to be minimal. In addition, there was medical interest in the possibility to offer to the population of sick children at large the option to benefit from the availability of small solid oral dosage forms such as mini-tablets. Thus, in conclusion, there was no benefit of the individual child by participating in the study while there was minimal risk and burden for the child in this study, however, benefit for all sick small children and thus the legally accepted group benefit for children was clearly given. This fact was well understood and supported by more than 50% of the sick children's parents approached for participation in this study.

The acceptance of the suitability of solid oral dosage forms, especially for children under the age of 6 years, was differently seen by paediatric experts from WHO and EMA. In EMA's Reflection Paper efforts had been made to suggest suitable age ranges for the definition of recommended dosage forms. While administration of solid oral dosage forms was considered as "not applicable" for children between 1 month and 2 years, their administration was considered "probably acceptable but not preferred" at the age of 2-5 years, and only at the age above 5 years their administration was rated from "good applicability" to "best and preferred applicability".

Based on public comments on the Reflection Paper the EMA focused their suitability assessment in their first "Draft Guideline on pharmaceutical development of medicines for paediatric use" on the size of solid oral dosage

forms and stated that small tablets of e.g. 3-5 mm could be acceptable for young children but not for children below the age of two years. They further elaborated that the suitability of solid oral dosage forms might also be "dependent of the disease and the risks of under-dosing, choking and aspiration" and that "any identified risk should be carefully balanced against the risks associated with the application of an alternative dosage form".

In the second draft of this Guideline, based on further public comments and provision of the pilot study results from the Heinrich-Heine University research group the attempt to assign the suitability of a solid oral dosage form to a specified age range was abolished. Instead, balanced comments like "oral solid single-unit dosage forms may provide a stable and easy dose approach. However, where individually adapted dosing is necessary the number of strengths that are needed to treat patients in the target age group(s) will increase. Alternatives which may provide dosing flexibility for tablets include addition of score lines enabling the administration of a fraction of the full tablet dose or (small) tablets containing only a fraction of the required dose which may be taken simultaneously to deliver the required dose." It was recommended that "the acceptability of the size and shape of the tablets by the target age group(s) should be justified, and supported by appropriate studies or clinical evidence, where relevant". In the final version of the guideline these points of view have not changed.

WHO, ICH-E11 and EMA proposed to investigate new medicines in children in 3, 5 or 6 different age groups, respectively, to acknowledge the differences in systems and process maturation. However, even the 6 age groups proposed by the EMA provide only a rough frame, especially for the rapidly developing deglutition maturation process and the acceptance of different galenic formulations. To be able to identify as precisely as possible potential differences in the acceptability and capability to swallow solid oral dosage forms, a more detailed age classification was chosen in this study with the youngest group comprising only 6-12 months and then yearly steps until the age of 6 years. At this stage the deglutition process is proven to be adult-like.

Only limited guidance on a suitable approach to investigation of mini-tablets in different age groups was available in literature. Thomson et al. only started their research in children of 2 years, without a control group and with a sample size only allowing for descriptive evaluation. Especially data on the younger age groups' (6 to 12 months and 1 to 2 years) acceptability and capability to swallow were of particular relevance when investigating potential differences. As this study included mini-tablets of 2 mm diameter and not 3 mm as in Thomson et al.'s study the risk of exposing so small children to the study procedures was considered minimal.

To generate reliable data on the children's acceptability of mini-tablets in comparison to syrup it was necessary to perform a confirmatory clinical trial

with a sufficiently large patient population to identify statistical differences. However, no variability data were available to calculate the required sample size. Therefore, a pilot study (Attachment 7.8) with 60 patients was performed first, including the 6 age groups planned in the confirmatory study. This pilot study also allowed investigating the suitability of the study procedures like deglutition success evaluation and assessment criteria. Thorough, standardized oral inspection by the same investigators with torch and spattle before and after drug administration was considered to be the least burdensome approach for the children while providing reliable evidence of the completion of the deglutition act. Colour marking of the oral formulations for mouth and urinary inspection was not possible with cross-over administration of three different galenic formulations within one study day. This, however, was necessary to ensure the acceptance of the study conditions for children and parents. A parallel design would have required many more children to be exposed to the study risk and burden to achieve statistically significant results. An intra-individual comparison of the swallowing results as enabled by a three-way cross-over design reduced the variability of the data and enhanced their comparability. The study had to be performed in an open (unblinded) design due to the fact that the formulations had different appearance and anyway only contained placebo. Therefore, a double dummy technique – often applied in double-blind active ingredient studies – was not possible. The randomization of the three-way cross-over administration avoided the bias of sequence effects.

Of critical importance for the comparability of the findings and thus the relevance of the information generated in this study was the selection of the assessment criteria. Thomsen et al. used the assessment criteria

- swallowed
- chewed
- refused
- spat out

and only rated “swallowed” as proper acceptance of the child.

As the here presented study included smaller children the danger of aspiration existed and therefore these categories were expanded by a fifth category: “choked on”. The most important criterion for drug administration is the swallowing of the entire dose administered, independent of whether the child swallowed the formulation as a whole or first chewed on it. Thus, “swallowed” and “chewed” were both rated as “acceptable”, whereas “capability to swallow” was restricted to the category “swallowed” only. In line with the 5 categories for mini-tablets, 5 categories for the swallowing of the syrup had to be created, representing the children’s behavior, to enable comparison between both formulations. As some reviewers of the submitted publication expressed difficulties to understand the meaning and relevance of “choked on”, this term

was exchanged by the more explicit new term “inhaled/coughed” in the final version of the publication.

The selected categories proved to be suitable to identify differences between the administrations of the three formulations over all age groups as presented in the publication. But also in the age sub-group analysis these categories were distinctive: in a post-hoc evaluation of the statistical significance of the identified and described differences of acceptability and capability to swallow between the different formulations in the age sub-groups a pattern could be identified: despite the small sample sizes the acceptability of the uncoated mini-tablet was significantly better than that of the syrup in all age groups (age group 6-12 months: p=0.026; age group 2-3 years: p=0.003; age group 3-4 years: p=0.003; age group 4-5 years: p=0.049; age group 5-6 years: p= 0.008) with exception of the age group 1 to 2 years (p=0.089). For the “capability to swallow” rating such significant difference could only be demonstrated for the age group 4 to 5 years (p=0.002). Also for the coated mini-tablets versus syrup significant differences in acceptability could be detected: age group 1-2 years: p=0.008; age group 2-3 years: p=0.003; age group 3-4 years: p=0.003 and age group 5-6 years: p=0.005. As with the uncoated mini-tablets, only in the age group 4-5 years the category “capability to swallow” was significantly different from placebo: p=0.039.

Comparing the results of this study with the findings of the Thomsen et al. study a significant advantage in the acceptability of the mini-tablets by smaller than 4 year old children might be the size of the mini-tablet with a diameter of only 2 mm. This size, however, raised the debate with EMA whether the mini-tablets should be categorized as “mini-tablets” or “pellets”. 2 mm solid oral dosage forms can be manufactured in form of both, pellets or mini-tablets. The difference between pellets and mini-tablets is not a question of size but of the manufacturing process and the resulting shape: pellets are spherical granulates which can be manufactured in different processes. Mini-tablets, however, can only be manufactured by compressing powders or granulates and this results in convex surfaces and straight edges (38). The pressing process improves the precision of tablet manufacturing and thus of dosing.

Despite the fact that this confirmatory study was adequately designed and performed to provide reliable information on the acceptability of mini-tablets in small children, the current approach contains several weaknesses:

1. For logistical and ethical reasons the study was performed in an open (non-blinded) design. However, this increased the potential for an investigator and patient bias.
2. The chosen evaluation criteria were relatively soft and not formally validated. The reliability of the study results was, however, improved by a standardized assessment procedure and limitation of the number of involved investigators.

3. The investigated age range was limited and did not include the most vulnerable and potentially most critical population of neonates and infants up to 6 months.
4. The study did not provide any information on the acceptability of administration of several mini-tablets for a single dose or repeated doses.
5. There was no active substance in the mini-tablets and thus the proof of efficacy of the mini-tablets was not provided with this study.
6. As there were no active substance-containing mini-tablets investigated, this study did not allow the collection of drug substance-related safety data for the mini-tablets. Due to the limited number of patients involved also the information on tolerability is limited.

Further studies will be required to provide information on the acceptability in newborns and infants up to 6 months of age. Furthermore, in children of all age groups as well as in adolescents, the acceptability of several mini-tablets and the efficacy and safety of mini-tablets with active ingredients in several areas of indication need to be investigated.

5. Conclusion

This properly designed and executed confirmatory study with single administration of two different types of placebo-containing mini-tablets in comparison to syrup allowed to reliably assess the differences in acceptability and capability to swallow of the two solid formulations in comparison to the present “gold standard” syrup.

The acceptability and capability to swallow of both, the uncoated and coated mini-tablets, were statistically superior to syrup over all age groups investigated.

Despite the small sample sizes the sub-group analysis of the acceptability of the coated and uncoated mini-tablets showed a statistically significant superiority of the mini-tablets in nearly all age groups in comparison to syrup.

The chosen methodology proved to be solid enough to distinguish the effects between test medication and comparator.

Both conducted studies, the exploratory and the present confirmatory study, provide justification for administering small-sized tablets to children from six months to six years.

This study provided reliable data to the EMA to support their revised draft guideline on pharmaceutical development of medicines for paediatric use and hence stimulate pharma industry to explore further applications of mini-tablets.

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7. Attachments

7.1 Study protocol “Randomized, Cross-over Physiological Examination of Acceptability and Capability to Swallow Three Oral Placebo Formulations for Children of Six Different Age Groups”, Protocol Number: 2010 – 001, 25.10.2010

7.2 Ethics committee vote, 02.02.2011

7.3 GCP certificate from Viviane Klingmann

7.4 Patient information sheet

7.5 Informed consent form

7.6 Comic

7.7 Assent

7.8 Publication of the pilot study, “Acceptance of uncoated mini-tablets in young children: results from a prospective exploratory cross-over study”, Spomer N, Klingmann V, Stoltenberg I, Lerch C, Meissner T, Breitkreutz J., published in Archives of Disease in Childhood, March 2012; 97(3): 283-6

7.1 Study protocol “Randomized, Cross-over Physiological Examination of Acceptability and Capability to Swallow Three Oral Placebo Formulations for Children of Six Different Age Groups”, Protocol Number: 2010 – 001, 25.10.2010

Protocol

(Dokument 3.1.1)

Randomized, Cross-over Physiological Examination of Acceptability and Capability to Swallow Three Oral Placebo Formulations for Children of Six Different Age Groups

Protocol Number: 2010 – 001 (Version 1)

Register Number: will be registered in "Deutsches Register Klinischer Studien"

Principal Investigator:
PD Dr. med. Thomas Meissner
Universitätsklinik Düsseldorf
Klinik fürAllgemeine Pädiatrie
Moorenstraße 5
40225 Düsseldorf

In collaboration with:
Prof. Dr. Jörg Breitkreutz
Heinrich-Heine Universität
Institut für Pharmazeutische Technologie und Biopharmazie
Universitätsstraße 1
40225 Düsseldorf

Düsseldorf, 25.10.2010

Confidential

Summary Information

Title:	Randomized, Cross-over Physiological Examination of Acceptability and Capability to Swallow Three Oral Placebo Formulations for Children of Six Different Age Groups
Protocol Number:	2010-001
Principal Investigator:	PD Dr. med. Thomas Meissner Universitätsklinik Düsseldorf Klinik für Allgemeine Pädiatrie Moorenstraße 5 40225 Düsseldorf
Protocol Authors and Co-Investigators:	Viviane Klingmann Natalie Spomer
In Collaboration with:	Prof. Dr. Jörg Breitkreutz Heinrich-Heine Universität Düsseldorf Institut für Pharmazeutische Technologie und Biopharmazie Universitätsstraße 1 40225 Düsseldorf
Statistician:	Dr. Christian Lerch Cochrane Metabolic and Endocrine Disorders Group Abteilung für Allgemeinmedizin Universitätsklinikum Düsseldorf Moorenstraße 5 40225 Düsseldorf

Placebo Formulations and Manufacturers:

Minitablet ø 2mm uncoated
Manufacturer: Institut für Pharmazeutische Technologie und Biopharmazie
Heinrich-Heine Universität Düsseldorf
Universitätsstr. 1
40225 Düsseldorf

Minitablet ø 2mm coated
Manufacturer: Institut für Pharmazeutische Technologie und Biopharmazie
Heinrich-Heine Universität Düsseldorf
Universitätsstr. 1
40225 Düsseldorf

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

Signatures:

…….. ……..
PD Dr. Thomas Meissner Date
Principal Investigator

……. …….
Viviane Klingmann Date
Protocol Author&Co-Investigator

……. …….
Natalie Spomer Date
Protocol Author&Co-Investigator

……. …….
Prof. Dr. Jörg Breitkreutz Date

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Glossary

AE	Adverse Event Adverse
AMG	Arzneimittelgesetz
CDMS	Clinical Data Management System
CRF	Case Report Form
ø	Diameter
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
℃	Grad Celsius
HIV	Human Immunodeficiency Virus
IEC	Independent Ethics Committee
KKS	Koordinationzentrum für Klinisch Studien
mm	Millimetre (s)
ml	Millilitre (s)
N	Number
SAE	Serious Adverse Event
SUSAR	Unexpected Serious Adverse Reactions
Q1	First Quartile
Q3	Third Quartile

1 Synopsis

1.1 Title

Randomized, Cross-over Physiological Examination of Acceptability and Capability to Swallow Three Oral Placebo Formulations for Children of Six Different Age Groups

1.2 Objectives

1.2.1 Primary Objectives

To prove that the acceptability of the uncoated minitablet is superior to the acceptability of the syrup in the group of children between 0.5 and 5 years inclusive.

1.2.2 Secondary Objectives

To prove that children are able to swallow a solid formulation as well as a liquid.

To investigate the differences in the acceptability of the uncoated minitablet versus the syrup in each age group.

To investigate the differences in the acceptability of the coated minitablet versus the uncoated minitablet in each age group as well as for the whole population.

To investigate the differences in the acceptability of the coated minitablet versus the syrup in each age group as well as for the whole population.

To investigate the differences in the capability to swallow three different oral placebo formulations in each age group as well as in the whole population.

To identify the differences in percentage of children in the different age groups who choke on any of the three oral placebo formulations.

To identify the number of children who refuse to take an oral placebo formulation or who spit it out.

To identify any possible problem, that could occur during deglutition.

To show that children beginning at the age of six months are capable of swallowing a solid oral formulation.

To analyse the compliance of children requested to swallow a minitablet or glucose-syrup.

To identify the difference in palatability of the three oral placebo formulations.

To investigate the safety of all oral placebo formulations.

1.3 Design

This physiological examination will be performed in a single-centre, open, randomised, single dose, three-way cross-over design.

1.4 Population

The parents of approximately 700 children, aged between 0.5 and 5 years inclusive, will be approached. Those children who satisfy all in-/exclusion criteria according to the judgement of the treating physician at the paediatric hospital will be scheduled for the physiological examination. In total 306 paediatric patients in six age groups that meet the in-/exclusion criteria will be enrolled and randomised to the order of the application of the three oral placebo formulations.

1.5 Formulations under Examination

Minitablet ø 2mm uncoated
Minitablet ø 2mm coated
Glucose-Syrup 15%, 3 ml

1.6 Examination Plan

After having received the written Informed Consent and the Assent from parents respectively children, the in- and exclusion criteria will be assessed and those children suitable for enrolment into the physiological examination will be randomised to the sequence of placebo formulations according to the randomisation scheme. After an oral inspection the children will receive either the uncoated minitablet with a drink of their choice or the coated minitablet with a drink of their choice or 3 ml of the glucose-syrup. The process of deglutition will be observed and the result of swallowing assessed by oral inspection. As soon as the child is ready for the second respectively the third part of the examination, the administration and assessment procedure will be repeated with the other formulations. The following evaluation criteria will be assessed:

<u>Minitablet uncoated and coated:</u>

- 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 was swallowed
    - which means that no liquid was left in the mouth and no drops left the mouth
    - interpreted as accepted and swallowed
- Small runlet was flowing out of the mouth or leftover on the spoon or the pipette
    - 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 pipette or the teaspoon 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

1.7 Duration and Timings

The duration per child will comprise maximally 2 days of activity: parents and children interested in participating in the physiological examination and where the child fulfilled the inclusion and exclusion criteria according to the treating physician at the hospital will be invited to a participant information and Informed Consent/Assent session. After signing the Informed Consent/Assent, the child will enter the physiological examination. After another verification of the in- and exclusion criteria the three formulations will be applied within 15 minutes. After complete assessment and verification of the child's wellbeing, the child will be released from the physiological examination.

1.8 Statistical Evaluation

1.8.1 Sample Size

The primary objective guided the sample size calculation for this study. Based on the results of the pilot study (Protocol number 2009-001), the overall proportion of children able to swallow the control 'syrup' is assumed to be 78%. The proportion of children able to swallow the investigated intervention 'uncoated 2 mm mini tablet' is assumed to be 10 percentage points higher (that is 88%). Based on the sample size formula approach of Schouten and Kester[12] and accounting for equal sample sizes for each of the six age-based subgroups, 306 participants need to be investigated. The two-sided α will be set at 0.05.

1.8.2 Statistical analysis

The primary objective will be investigated using the approach of Schouten and Kester[12]. The evaluation of the secondary objectives will occur in form of descriptive statistics with number of observations, arithmetic mean, minimum, Q1, median, Q3, maximum. A generalised mixed-effects model will be applied. Additionally, they will be analysed by estimating the respective success proportions and their 95%-confidence intervals (accounting for the clustered nature of data).

1.9 Reporting

This physiological examination will be registered in the “Deutsches Register Klinischer Studien”. The results will be reported in form of a medical dissertation of the two protocol authors and publication will be sought in form of a poster at a scientific congress and in a well established journal.

2 Introduction

Children are not small adults, and nowhere can this be considered more important than in the development and use of medicines for children.[1] So far, over 60% of treatments in children are off-label[2]. A study performed in 5 European paediatric hospitals and published in 2000 revealed that two thirds of the paediatric in-house patients received medication that had no marketing authorisation in this country or in this indication[3]. Only 15 of 110 new drugs centrally authorised by the European Medicines Agency in 2000 contained paediatric data despite the fact that 49 of them involved indications of paediatric relevance[4]. This required urgent change but pharmaceutical industry was not interested in heavily investing in the development of paediatric treatments as the markets are small and incentives were lacking. Before a new medicinal product for human use is placed on the market, it has to have undergone extensive studies, 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 proven suitable treatments results in the administration of potentially inadequate substances and doses. This leads to an increased risk of insufficient treatment and adverse reactions including death and often deprives children from benefiting from therapeutic advances. Current practice of administration of liquids and syrup has been reported to result in surprisingly unreliable dosing potentially leading to substantial under- or over-dosage[5]. 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.

With implementation of the new European Paediatric Regulation (Regulation (EC) No 1901/2006, "Better medicines for children")[6] in 2006 European and national legislators wanted to create the 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 the Paediatric Regulation dramatically changed the regulatory environment for paediatric medicines in Europe: the Paediatric Regulation requires that European marketing authorisation for new medications can only be achieved if the sponsor company provides data on use of this new drug in children. In 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 requires as well that suitable

paediatric formulations are to be developed to ensure adequate dosing and administration of the drugs.

The 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 means that frequently a different formulation (e.g. liquid, suppository) has to be chosen. 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 strong advantages by avoiding the problems with stability, storage conditions[2], taste-masking[8] and exact dosing that liquids present. However, in literature there is no scientifically sound information on acceptability 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. Because of a lack of studies surveying the use of different formulations for children, understanding of the ability of children to swallow orally administered solids still seems to be based on perception rather than evidence [8].

But also in 2010 the problems are not solved: Krause and Breitkreutz[9] published an overview of the current stage of paediatric formulation development: "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 newborns 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."

The EMA Reflection Paper "Formulations of Choice for the Paediatric Population" [7], published in 2006, provides a summary of the current stage of knowledge on paediatric formulations and comes 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 further provides 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 describes advantages of buccal/sublingual administration

- buccal and sublingual tablets
- muco-adhesive preparations

as well as nasal administration (drops, spray, or powder), rectal, trans-dermal, pulmonary and parenteral administration.

It concludes that very few information from literature 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 provides a table of recommended dosage forms per age group.

To increase the safety and reliability of oral paediatric treatment and to generate the basis for comparisons with other paediatric administration routes it is important to generate scientifically solid physiological information on acceptability and capability of children, especially in young age, to swallow liquid and solid oral dosage forms.

In clinical practice syrup is the most frequently used formulation, but also a specially designed minitablet has advantages as it is easy in handling and a cheap alternative. But only one study has been performed to evaluate its suitability for children. This pilot study "Minitablets: New Modality to Deliver Medicines to Preschool-Aged Children" [8] demonstrates the acceptability but not the capability of preschool-aged children to swallow 3 mm diameter minitablets. Further research is required on capability to swallow and acceptability of smaller solid oral formulations by younger children.

To be able to develop hypotheses for a properly designed and powered clinical trial on the acceptability and capability to swallow different oral formulations of children of all age groups between 0.5 to 5 years it was necessary to generate data on those parameters for syrup and a potentially suitable solid oral formulation like an uncoated

2 mm minitablet in a pilot study. The cut-off age chosen in this physiological examination was at the age of five years inclusive as it has been demonstrated that by the age of six years, children have adult-like control during swallowing [10]. This pilot study, performed at the Paediatric Clinic of the University Hospital of Düsseldorf in 2010 with 10 children in each age group provided sufficient data to calculate the sample size of this planned study. It gave first hints that the acceptability ("swallowed" and "chewed") of the uncoated minitablet was superior to the syrup in most of the investigated age groups.

3 Rationale

Due to the lack of scientifically sound data on the suitability of 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 physiological examination in a sufficiently large number of patients of the particularly vulnerable age groups, namely 0.5 to 5 years, comparing coated and uncoated oral minitablets with the current standard, the syrup. Acceptability and capability to swallow 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 the different age groups.

The main concern with oral formulations, especially in small children, is their ability to swallow solid formulations as very little physiological knowledge exists on the development and maturation of the deglutition act in small children. This physiological examination is supposed to assess the frequency of choking on solid and liquid formulation of children in the different age groups as a parameter for the maturity of the deglutition act.

The ICH E 11 guideline[11] 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 physiological examination 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 physiological examination a randomised three-way cross-over design is chosen as the cross-over pilot examination in 60 children performed with 2 different oral formulations has shown that repeated administration of 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 technically not be possible.

4 Ethics

4.1 Ethical Review

The final physiological examination protocol, including the final version of the Participant Information and Consent Form, must be given a favourable opinion in

writing by an Independent Ethics Committee (IEC) before the enrolment of any participant into the physiological examination. The Principal Investigator will also be responsible for seeking favourable opinion from the IEC of any substantial amendment to the protocol.

4.2 Ethical Conduct of the Physiological Examination

The physiological examination 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 physiological examination does not fall under the German "Arzneimittelgesetz (AMG)" because it does not include the application of any investigational medicinal product as defined in the AMG. Paediatric patients participating in this physiological examination will have no direct benefit from their participation but their participation will help future children requiring adequate dosing and application of medical treatment.

The monitoring of this physiological examination is applied at Koordienierungszentrum für Klinische Studien (KKS) 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 physiological examination. Parents must also be notified that they are free to withdraw their child from the examination at any time. The parents should be given an opportunity to ask questions and get time for consideration. The participant's signed Informed Parental Consent has to be obtained prior to any activity related to the physiological examination. The original must be stored by the Principal Investigator. A copy of the Parent Participant Information including the signed Parental Consent Form should be given to the parents of the participant. The investigator, or designee, should note the date and time that the consent process was completed 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 should 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 physiological examination 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

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

5 Objectives

5.1 Primary Objectives

To prove that the acceptability of the uncoated minitablet is superior to the acceptability of the syrup in the group of children between 0.5 and 5 years inclusive.

5.2 Secondary Objectives

To prove that children are able to swallow a solid formulation as well as a liquid.

To investigate the differences in the acceptability of the uncoated minitablet versus the syrup in each age group.

To investigate the differences in the acceptability of the coated minitablet versus the uncoated minitablet in each age group as well as for the whole population.

To investigate the differences in the acceptability of the coated minitablet versus the syrup in each age group as well as for the whole population.

To investigate the differences in the capability to swallow three different oral placebo formulations in each age group as well as in the whole population.

To identify the differences in percentage of children in the different age groups who choke on any of the three oral placebo formulations.

To identify the number of children who refuse to take an oral placebo formulation or who spit it out.

To identify any possible problem, that could occur during deglutition.

To show that children beginning at the age of six months are capable of swallowing a solid oral formulation.

To analyse the compliance of children requested to swallow a minitablet or glucose-syrup.

To identify the difference in palatability of the three oral placebo formulations.

To investigate the safety of all oral placebo formulations.

6 Examination Plan

6.1 Design

This physiological examination will be performed in a single-centre, open, randomised, single dose, three-way cross-over design.

6.2 Population

6.2.1 Source and Number of Participants

The paediatric patients will be recruited in the Paediatric Clinic of the University Hospital Düsseldorf (inhouse and outpatient).
For the physiological examination a total of 306 evaluable children will be required. To ensure 306 evaluable children it is assumed that 700 children will have to be approached.

6.2.2 Inclusion Criteria

1. Age
Children aged from 0.5 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
Participants suffering from illness must be able to swallow in the opinion of the Principal Investigator based on medical history, physical examination and all other appropriate diagnostic procedures.

5. Compliance
Participant and participant's 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 physiological examination and have given written informed consent.

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. 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 eat and capable to follow the physiological examination-related instructions.

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

6.2.4 Participants Withdrawal Criteria

Participants 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 a 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.

6.2.6 Participants Restriction

Participants are asked to avoid eating within one hour before the physiological examination.

6.3 Clinical Supplies

6.3.1 Formulations for the Physiological Examination

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

A) Minitablet ø 2mm uncoated: 1 minitablet per child and intervention
B) Minitablet ø 2mm coated: 1 minitablet per child and intervention
C) Glucose-Syrup 15%: 3ml glucose-syrup per child and intervention

A) Manufacturer: Institut für Pharmazeutische Technologie und Biopharmazie
Heinrich-Heine Universität Düsseldorf
Ingredients: - Lactose
- Cellulose
- Magnesium stearate

- Anhydrous colloidal silicon dioxide

B) Manufacturer: Institut für Pharmazeutische Technologie und Biopharmazie
Heinrich-Heine Universität Düsseldorf
Ingredients: - Lactose
- Cellulose
- Magnesium stearate
- Anhydrous colloidal silicon dioxide
- Coating:
Pharmacoat 606 (Hypromellose)
Macrogol 1500

C) Manufacturer: Caesar & Loretz GmbH
Ingredients: - Glucose 250g
- Water 37,5g

6.3.2 Packaging and Labelling

Minitablets will be provided in a glass in bulk.
The glucose-syrup will be delivered in glass bottles.

6.3.3 Accountability of Examination Supplies

All material supplied will be for use only in this physiological examination 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 rendered to the “Institut für Pharmazeutische Technologie und Biopharmazie” of the Heinrich-Heine University Düsseldorf”.

6.3.4 Storage of Clinical Supplies

Clinical supplies must be stored in compliance with the label requirements at room temperature between 15℃ - 25℃ 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 physiological examination, the child's both parents will be required to give written informed consent and the children their assent as far as possible before any examination-related procedures are 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

306 children, male and female, aged from 0.5 to 5 years will be recruited. They will be stratified into six age groups:

1. 0,5 – 1 year
2. 1 – 2 years
3. 2 – 3 years
4. 3 – 4 years
5. 4 – 5 years
6. 5 – 6 years

In the physiological examination each stratum will contain 51 children. There will be no fixed ratio between male and female children per age group.

The children in each age group will be randomised to an application sequence for the three different formulations according to the randomisation scheme. Randomisation will be provided for at least 400 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 parents will be seated in a quiet, distraction-free area.
The Investigator will review all provided information and the judgement on the child's suitability for the physiological examination provided by the referring physician. 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.

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 minitablet will be placed on the tongue and the child will be asked to put the tongue back into the mouth. If the child is not capable to follow the instructions, the minitablet will be applied with a teaspoon.
The participant has to swallow the minitablet with up to three mouthfuls of a drink of his/her choice.

The glucose-syrup is either given with a pipette in a slightly opened mouth or with a teaspoon depending on the child's capability to understand the instructions. The glucose-syrup has to be swallowed without any additional liquid.

The deglutition process will be thoroughly observed by the investigator. After deglutition the mouth of the participant will be inspected by the investigator and the result as well as the result of the observation of the deglutition process assessed according the criteria described in Section 7.1 "Physiological Evaluation Variables" and recorded in the CRF. Any adverse events observed and reported will be assessed and documented as well according the criteria described in Section 7.2 "Safety Variables".

In the second part the process will be repeated with one of the other formulations. In the third part the process will be repeated with the remaining formulation within 15 minutes.

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.

7 Evaluation Criteria

7.1 Physiological Evaluation Variables

7.1.1 Minitablet uncoated and coated:

- 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

7.1.2 Glucose-syrup

- Everything was swallowed
    - which means that no liquid was left in the mouth and no drops left the mouth
    - interpreted as accepted and swallowed
- Small runlet was flowing out of the mouth or leftover on the spoon or in the pipette
    - 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 pipette or the teaspoon 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

7.2 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 pilot examination with 60 children no single case of aspiration has been observed. Yet, all possible efforts will be made to minimise this risk: the physiological examinations 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. An additional safety factor is the fact that the uncoated minitablet is soluble in the mouth within seconds and the coated minitablet within few minutes.

7.2.2 Adverse Events

All adverse events encountered during the physiological examination, whether spontaneously reported by the participant at any time during the examination or elicited by the investigator in a standard manner, will be reported in the CRF.

The investigator or designee must ask the participant the following question after each examination: **"Do you feel unwell or have you experienced any symptoms?"**

All adverse events encountered during the physiological examination will be reported in the CRF. An Adverse Event (AE) is any untoward medical occurrence in a participant administered an oral formulation and which does not necessarily have to have a casual relationship with this application. 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, an AE can be any unintended change (including physiological, psychological or behavioural) from the time a participant has given informed consent, including intercurrent illness, which occurs during the course of a physiological examination.

Clinical 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.

Examination relationship for each adverse event should be determined by the investigator using the following explanations:

- 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 physiological examination, 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 designee 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);

- 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 an 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 24 hours, 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 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

This study is both a confirmatory and an exploratory study aiming at investigating the capability of children of different age groups to swallow three different oral placebo formulations after single-dose administration. The confirmatory part addresses the primary study objective; the investigation of all secondary study objectives will be considered as exploratory and interpreted accordingly. The statistical analysis will be carried out by Dr. Christian Lerch, M Clin Epid (University of Newcastle), Cochrane Metabolic and Endocrine Disorders Group, using the software packages R and Stata.

8.1 Sample Size

The primary objective guided the sample size calculation for this study. Based on the results of the pilot study (Protocol number 2009-001), the overall proportion of children able to swallow the control ‘syrup’ is assumed to be 78%. The proportion of children able to swallow the investigated intervention ‘uncoated 2 mm mini tablet’ is assumed to be 10 percentage points higher (that is 88%). Based on the sample size formula (given by Schouten H and Kester A) [12], and accounting for equal sample sizes for each of the six age-based subgroups, 306 participants need to be investigated. The two-sided α will be set at 0.05.

8.2 Populations, Demographics

The data of all participants who will be enrolled into the study and who receive at least one formulation will be presented and discussed (full analysis set). The statistical analysis will be performed as a valid case analysis including all participants who have no major protocol deviations (per protocol set). The number of participants randomised, administered, had the assessments and completed the examination will be displayed by age group. Similarly, all protocol deviations will be listed and their possible influence on the results will be discussed. If a participant is to be excluded from the statistical evaluation, this decision has to be justified in the final report. The analysis of safety will be based on the full analysis set.
Drop-outs will be replaced. Missing values will not be imputed.

8.3 Statistical analysis

The primary objective will be investigated using the approach of Schouten and Kester. The evaluation of the secondary objectives will occur in form of descriptive statistics with number of observations, arithmetic mean, minimum, Q1, median, Q3, maximum. A generalised mixed-effects model will be applied. All secondary objectives will be additionally analysed by estimating the respective success proportions and their 95%-confidence intervals (accounting for the clustered nature of data).

9 Documentation, CRFs, and Record Keeping

9.1 Investigator's Files/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 separate categories (1) physiological examination master file, and (2) participant clinical source documents.

The physiological examination master file will contain the protocol/amendments, case report and query forms, IEC, informed consent, staff curriculum vitae, and authorisation forms and other appropriate documents/correspondence, etc.

The paper CRF will be used as source document as far as possible. Other source documents would include /participant hospital/clinic records, physician's and nurse's notes, appointment book and special assessment reports, physician's letters, screening and enrolment logs, 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 participant identification codes on file for at least 10 years after completion or discontinuation of the examination.

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 can not 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, a paper CRF must be completed with black ball-pen and signed by the Principal Investigator to certify that the data within each CRF are complete and correct. If a participant is withdrawn from

the examination because of an adverse event, thorough efforts should be clearly made to document the outcome.

All forms should be filled out during (or immediately after) a participant assessment, and must be complete 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 paper CRFs, which will be transcribed to the eCRF by the sites personnel (investigator or assistant personnel). The query management is performed electronically. Any queries arising from data entry will be checked with the investigator and amendments approved. Databases will be checked for internal consistency and critical data compared with original CRF's.
The collected data that are transferred to the coordinating centre will only include pseudonymised data. The connection is secured by SSL-technology. Archiving of the clinical database including the audit trail can be provided by the coordinating centre in a machine independent format. Sites can be provided with an electronic CRF of their participants if necessary at study termination. After database lock data can be immediately 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 which alter the scope of the investigation, the scientific quality of the examination, the experimental design, frequency of administration, assessment variables, the number of participants enroled, 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 to the protocol will be will be submitted by the Principal Investigator to the Ethics Committee for favourable opinion. Non-substantial amendments will be filed in the Physiological Examination Master File.

11 Conditions for Terminating the Physiological Examination

The Principal Investigator reserves the right to terminate the physiological examination 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 participant's interests.

12 Confidentiality of Examination Documents and Participant Records

The investigator must assure that the participant's anonymity will be maintained. On CRFs or other documents submitted to the KKS Düsseldorf, participants should not be identified by their names, but by an identification code.

The investigator should keep a separate log of participants' codes, names and addresses. Documents not for submission to KKS Düsseldorf, e.g. participants' written consent forms, should be maintained by the Principal Investigator in strict confidence.

13 Publication of Data and Protection of Trade Secrets

The results of this physiological examination will be presented in the "Deutsches Register Klinischer Studien". The results will be reported in form of a medical dissertation of the two protocol authors and publication will be sought in form of poster at a scientific congress and in a well established journal.

14 References

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6. Paediatric Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006, on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004; published in the Official Journal of the European Union
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7.2 Ethics committee vote, 02.02.2011

HEINRICH HEINE
UNIVERSITÄT DÜSSELDORF

ETHIKKOMMISSION der Medizinischen Fakultät

ETHIKKOMMISSION der Medizinischen Fakultät der Heinrich-Heine-Universität, Moorenstr. 5, 40225 Düsseldorf

Herrn
Priv.-Doz. Dr. med. Meissner
Klinik für Allgemeine Pädiatrie

HIER

Prof. Dr. T. Hohlfeld

Telefon: (0211)81-19590
Sekretariat: (0211)81-19591
Telex: (0211)81-19592
Ethikkommission@med.uni-duesseldorf.de

02. Feb. 2011

Stets angeben:
Studiennummer: 3495

Sehr geehrter Herr Kollege Meissner,

die Ethikkommission der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf hat das von Ihnen vorgelegte Studienprotokoll mit dem Titel:

Randomized, cross-over, physiological examination of acceptibility and capability to swallow three oral placebo formulations for children of six different age groups

im Umlaufverfahren geprüft und beurteilt.

Von Seiten der Kommission bestehen keine ethischen oder rechtlichen Bedenken gegen die Durchführung der geplanten Studie. Die Ethikkommission bittet jedoch um Vorlage der noch fehlenden Probandenversicherung und Ergänzung diesbezüglich in der Teilnehmerinformation.

Nach Abschluss des Projektes bitte ich um Übersendung eines knappen Schlussberichtes oder einer abschließenden Publikation.

Für die Durchführung der Studie wünschen wir viel Erfolg!

Mit freundlichen Grüßen

[redacted]

Prof. Dr. med. Hohlfeld
i.A. der Kommission

Rechtsmittelbelehrung: Gegen diesen Bescheid kann innerhalb eines Monats nach Bekanntgabe Widerspruch erhoben werden. Der Widerspruch ist beim Dekan der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf schriftlich einzulegen.

7.3 GCP certificate from Viviane Klingmann

CERTIFICATE OF ATTENDANCE

EFGCP In-house GCP Training Course for Experienced Researchers

5 Jahre Erfahrung mit der EU Clinical Trial Directive und deren Bedeutung für Ihre Studiendurchführung

To whom it may concern:

We confirm that **Viviane Klingmann, Varnhagenstr. 38, 40225 Düsseldorf**

participated to the above 8 hour-GCP Training Course given on 10 October 2009 in the premises of FOCUS Clinical Drug Development in Neuss, Germany.

Referent: Dr. med. Ingrid Klingmann, FFPM, FBCPM
EFGCP Consultant & Trainer
Conference Officer & Co-Chairperson, Ethics Working Party / Patients' Roadmap to Treatment Working Party

Neuss, 10 October 2009

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7.4 Patient information sheet

Teilnehmerinformation

für

„Physiologische Untersuchung zur Akzeptanz und Schluckbarkeit von drei verschiedenen oralen Plazebo-Darreichungsformen bei Kindern verschiedener Altersgruppen“

Sehr geehrte Eltern,

Für viele Medikamente, die kranken Kindern helfen, haben die Ärzte keine wissenschaftlichen Informationen darüber, welche Dosen eigentlich die richtigen für Kinder verschiedener Altersgruppen sind, weil das nie untersucht wurde. Daher gibt es auch meistens keine 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 zwei verschiedenartige Minitabletten und ein Sirup an insgesamt 306 Kindern untersucht werden.

Die Probleme

Ein Problem ist, dass Sirups keine lange Haltbarkeit haben, wenn die Flasche mal geöffnet wurde und damit dann nicht mehr sicher abgeschätzt werden kann, welche Dosis des Medikaments Ihr Kind wirklich bekommt. Ausserdem werden Sirups von Kindern oft abgelehnt wegen des Geschmacks. 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 werden, um kleinere, für Kinder geeignete Mengen, zu erhalten. Dieses Vorgehen birgt die Gefahr, dass die gewünschte Dosis nicht korrekt ist, d.h. es kommt zu einer Über- oder Unterdosierung. Ausserdem sind diese Partikel vor allem für kleine Kinder schwierig zu schlucken. Eine mögliche Lösung stellen die neu entwickelten kindgerechten Minitabletten dar, die eine genaue Dosierung erlauben, vermutlich zuverlässig geschluckt werden können und die den bisher eingesetzten Sirup ablösen könnten. Da sich manche Tabletten erst im Magen auflösen sollten, damit die Wirkung voll zur Geltung kommt, müssen diese Tabletten mit einem Überzug versehen werden. Dies könnte aber einen Einfluss auf die Akzeptanz oder die Schluckbarkeit der Tablette haben.

Die physiologische Untersuchung

In dieser wissenschaftlichen Untersuchung soll nun erforscht werden, ob Kinder unter 6 Jahren in der Lage sind, solche speziell für Kinder entwickelten überzogenen und nicht überzogenen Minitabletten besser zu schlucken als einen Sirup, welche der Darreichungsformen sie eher akzeptieren und welche Darreichungsform für welche Altersgruppe am geeignetsten ist.

Ablauf der Untersuchung

Wenn Sie und Ihr Kind, soweit es das schon kann, in eine Teilnahme an dieser Untersuchung nach ausführlicher Aufklärung eingewilligt haben, wird Ihr Kind an drei Schluckversuchen innerhalb von 15 Minuten teilnehmen. Die Reihenfolge der verabreichten Dosierungsformen wird dabei von einer von einem Computer erstellten Zufallsliste festgelegt. Ihr Kind sollte eine Stunde vor Beginn der Untersuchung nichts gegessen haben.

Ihrem Kind wird dann zuerst entweder 3 ml eines nur Zucker enthaltenden Sirups mit einem Teelöffel oder einer Pipette (je nach Alter des Kindes) verabreicht oder eine der beiden Minitabletten mit einem Durchmesser von 2mm. Diese Minitabletten enthalten keinen Medikamenten-Wirkstoff (Placebo), sondern bestehen nur aus verschiedenen bei der Herstellung von Tabletten üblicherweise verwendeten Zuckern. Eine der beiden Minitabletten löst sich schnell im Mund auf, während die andere diese Eigenschaft nicht besitzt und daher vollständig geschluckt werden muss. Ihrem Kind werden die Minitabletten auf die Zunge gelegt und dann soll es diese Minitabletten mit jeweils maximal 3 Schlucken eines Getränks seiner Wahl hinunterschlucken.

Sobald das Kind bereit ist für den zweiten Schlucktest, wird eine der jeweils anderen Darreichungsformen verabreicht. Daraufhin folgt der dritte Schlucktest mit der noch verbleibenden Formulierung.

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

Die Untersucherinnen werden alle Beobachtungen sorgfältig dokumentieren. Die Auswertung der erhobenen Daten erfolgt am Koordinierungszentrum für Klinische Studien der Universität Düsseldorf.

Vorteile und Risiken

In einem persönlichen Gespräch werden Sie und Ihr Kind 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 beiden Darreichungsformen enthalten ist, aber dafür birgt diese Untersuchung auch nur minimale Risiken und bedeutet nur eine ganz geringe Belastund für Ihr Kind. Aber Sie helfen damit der Gruppe Millionen kranker Kinder in Zukunft eine zuverlässigere und akzeptablere Behandlung zu bekommen. Zu den möglichen Risiken zählt, dass sich Ihr Kind verschlucken und dabei sogar Atemnot entwickeln kann oder dass es zu einer allergischen Reaktion auf einen der Inhaltsstoffe kommen könnte. Die Untersucherinnen 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 wurde für die Kinder in dieser Untersuchung eine Versicherung bei der Zurich Gruppe (Poppelsdorfer Allee 25-33, 53115 Bonn, Nr. des Versicherungsscheins: 800.540.008.368) in Höhe von € 250 000 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 die oben genannten Minitabletten und den Zucker-Sirup 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.

7.5 Informed consent form

Einwilligungserklärung

Teilnahme an

„Physiologische Untersuchung zur Akzeptanz und Schluckbarkeit von drei verschiedenen oralen Plazebo-Darreichungsformen bei Kindern verschiedener Altersgruppen“

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. **Untersuchungsbezogene Teilnehmerdaten werden verschlüsselt und nur anonymisiert veröffentlicht und niemand ausser dem in die Untersuchung eingebundenen Personal wird Einblick in die Orginaldaten erhalten.**

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 Aufklärungsschreibens, unser Kind eine Kopie des Aufklärungs-Comics. Für Rückfragen steht auch der Untersuchungsleiter, Herr PD Dr. Thomas Meissner, jederzeit zur Verfügung.

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

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7.6 Comic

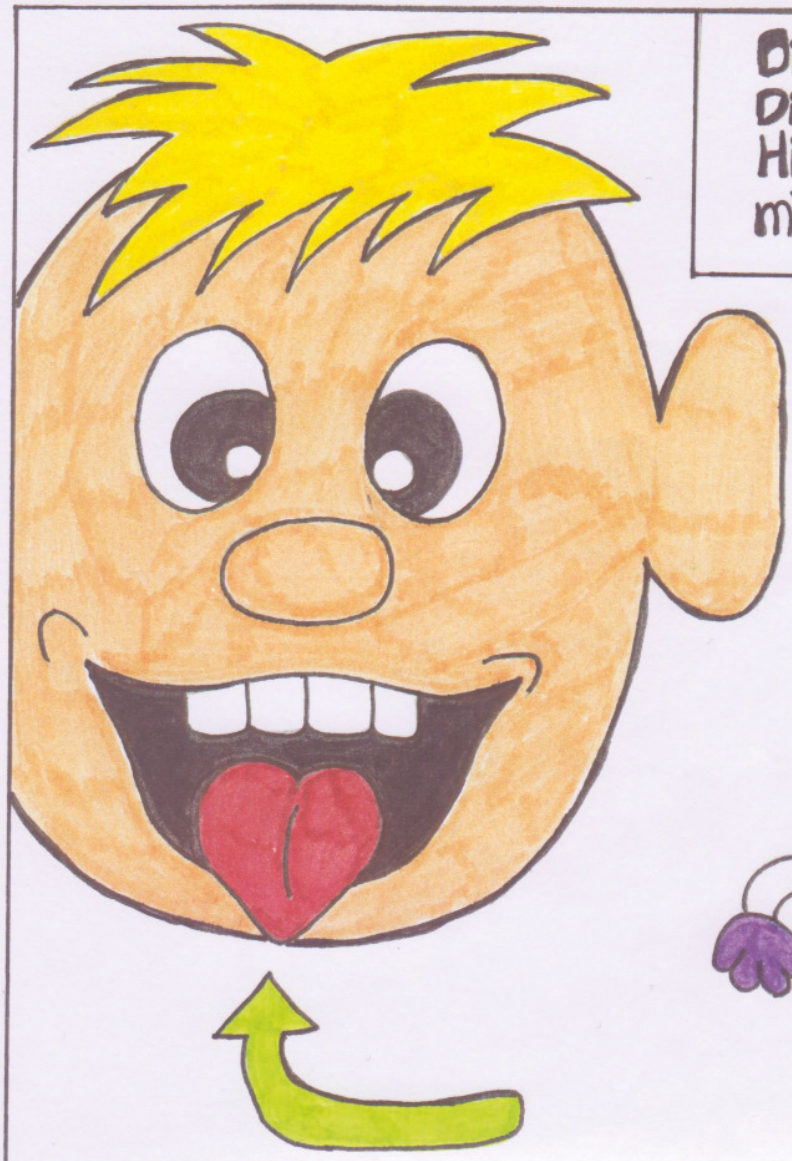
1

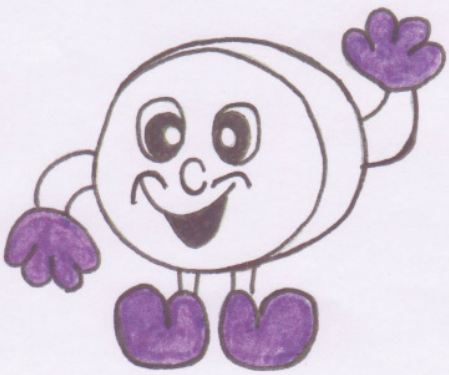
Hallo!

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.

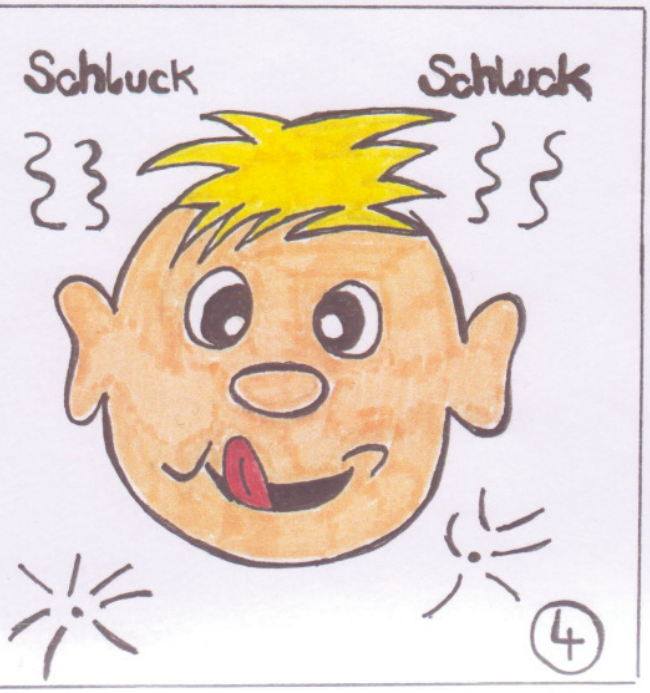


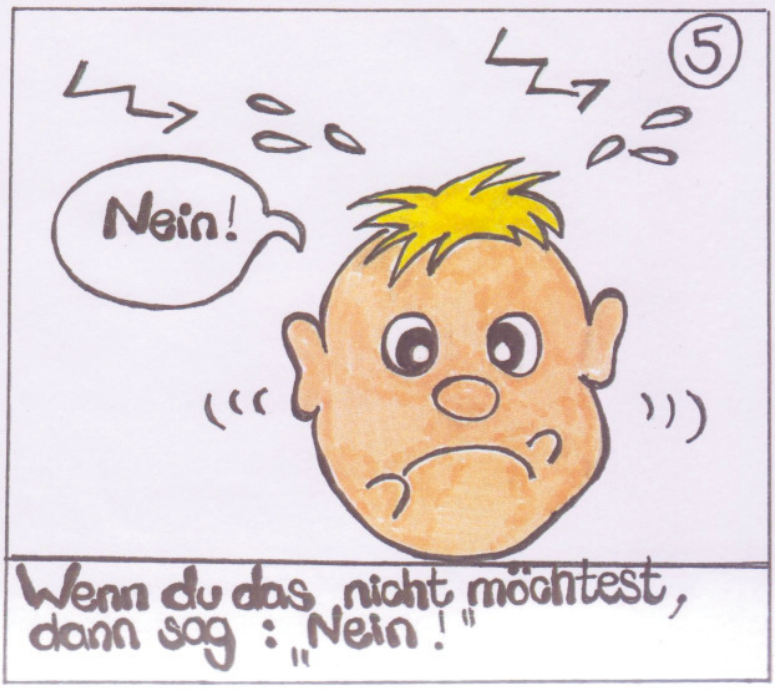


2

Nun darfst du auch etwas Leckeres trinken

③



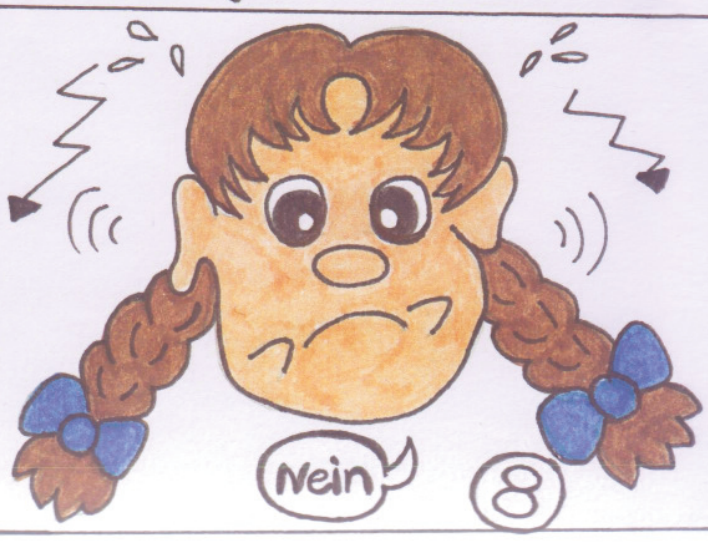


Hier siehst du, wie Sirup geschluckt wird. Danach darfst du aber nichts trinken.

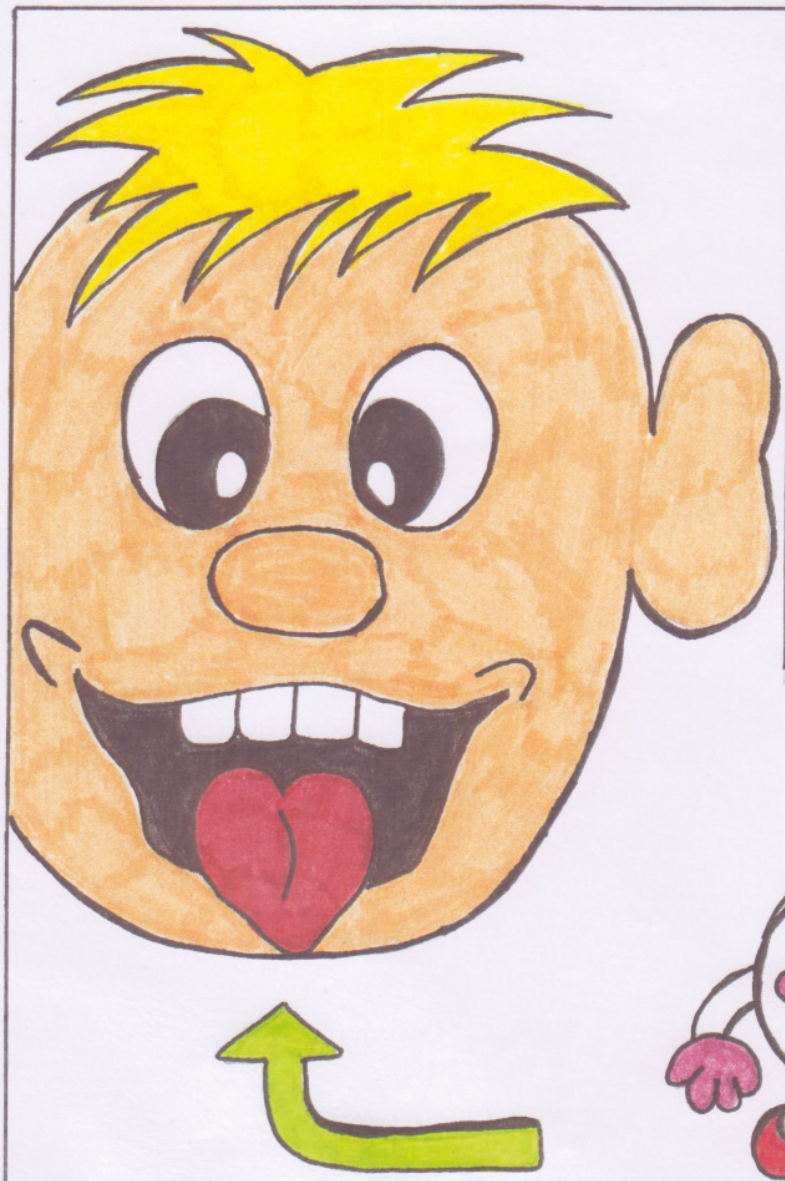
6

Schluck 7 Schluck

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

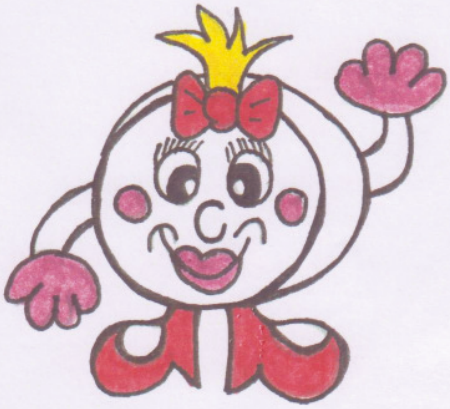


8



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

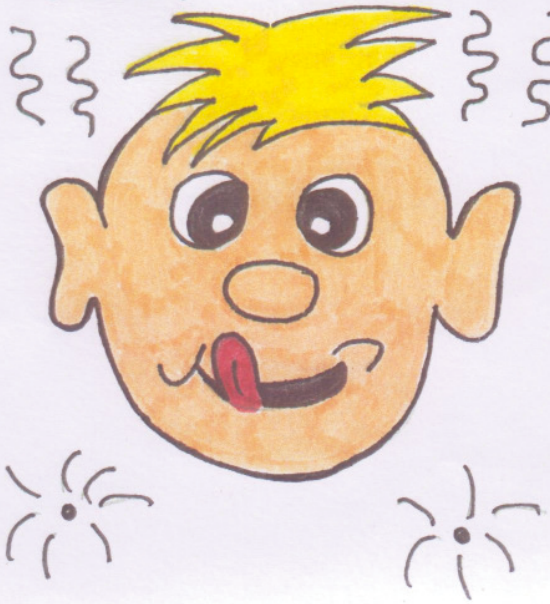
Die Reihenfolge in der du die drei Freunde bekommst, wird eine Überraschung



9

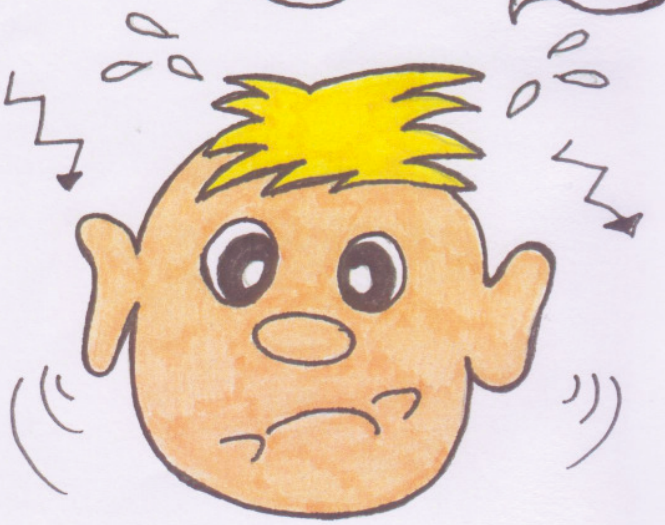
10

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, Tobea und Sirup auch nicht darin verstecken.

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

DANKE dass du mitmachst!

7.7 Assent

Einwilligungserklärung

Teilnahme an

„Physiologische Untersuchung der Akzeptanz und Schluckbarkeit von drei verschiedenen oralen Plazebo-Darreichungsformen bei Kindern verschiedener Altersgruppen“

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 wissenschaftliche Untersuchung 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 Herrn Dr. Thomas Meissner ansprechen.

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

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7.8 Publication of the pilot study, “Acceptance of uncoated mini-tablets in young children: results from a prospective exploratory cross-over study”, Spomer N, Klingmann V, Stoltenberg I, Lerch C, Meissner T, Breitkreutz J., published in Archives of Disease in Childhood, March 2012; 97(3): 283-6

Publikation:

Acceptance of uncoated mini-tablets in young children:

Results from a prospective exploratory cross-over study

Natalie Spomer, Viviane Klingmann, Ines Stoltenberg, Christian Lerch, Thomas Meissner, Jörg Breitkreutz

Archives of Disease in Childhood; 97(3): 283-286

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Eidesstattliche Versicherung

Ich versichere an Eides statt, dass die Dissertation selbstständig und ohne unzulässige fremde Hilfe erstellt worden ist und die hier vorgelegte Dissertation nicht von einer anderen Medizinischen Fakultät abgelehnt worden ist.

11.01.2014, Viviane Klingmann