

Supplementary Online Content

Mank E, Sáenz de Pipaón M, Lapillonne A, et al; FIT-04 Study Group. Efficacy and safety of enteral recombinant human insulin in preterm infants: a randomized clinical trial. *JAMA Pediatr*. Published online February 28, 2022. doi:10.1001/jamapediatrics.2022.0020

eTable 1. The FIT-04 Site Collaborators

eTable 2. Trial Steering Committee Members

eTable 3. Enteral Nutrition Recommendation in the Study Protocol (ESPGHAN guidelines)

eTable 4. Total Fluid (Enteral and Parenteral) and Nutritive Components

eTable 5. Prespecified Sensitivity Analysis of the Primary Outcome

eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. The FIT-04 Site Collaborators

The following hospitals, investigators, and research nurses participated in the FIT-04 trial. Study sites are listed alphabetically.

Country	City	Site name	Site collaborator name(s)
Belgium	Antwerpen	GZA campus Sint-Augustinus	Christine Vandeputte, MD Katleen Plaskie, MD
Belgium	Brugge	Algemeen Ziekenhuis Sint-Jan Brugge-Oostende AV	Luc M.G.I. Cornette, MD, PhD James D'haese, MD
Belgium	Brussel	Universitair Ziekenhuis Brussel	Filip Cools, MD, PhD Michel Sonnaert, MD
Belgium	Liège	CHC Clinique Saint-Vincent	Anne Vervoort, MD Pierre Maton, MD
Belgium	Liège	CHR de la Citadelle	Thibault Senterre, MD, PhD
Bulgaria	Pleven	University Hospital Dr. Georgi Stranski	Victoria G. Atanasova, MD, PhD Lyuben G. Veskov, MD
Bulgaria	Sofia	Specialized hospital for obstetrics and gynecology active treatment - Shejnovo	Donka P. Uzunova, MD Zornica T. Malinova, MD
France	Nancy	Maternité Régionale, CHRU de Nancy	Jean-Michel Hascoet, MD Emily Greze, MD
France	Paris	APHP Necker-Enfants Malades	Alexandre Lapillonne, MD, PhD Agnes Giuseppi, MD Virginie Rigourd, MD, PhD
France	Rennes	CHU Rennes, Hôpital Sud	Alain Beuchée, MD, PhD Nadia Mazille, MD
Germany	Berlin	Evangelisches Waldkrankenhaus Spandau	Frank Jochum, MD, PhD
Germany	Dresden	Klinik und Poliklinik für Kinder- und Jugendmedizin, Universitätsklinikum	Mario Rüdiger, MD, PhD Katrin Weber, MD
Germany	Pforzheim	Hospital Pforzheim	Walter A. Mihatsch, MD, PhD Rahel Schuler, MD
Hungary	Debrecen	DEKK Gyermekklinika Neonatológiai Intenzív Centrum	Andrea Nagy, MD Gergely Balázs, MD
Hungary	Szeged	Szegedi Tudományegyetem, Szent-Györgyi Albert Klinikai Központ, Perinatális Intenzív Centrum	Judit Kiss, MD Anna Gajda, MD
Hungary	Székesfehérvár	Szent György University Teaching Hospital of County Fejér	Hajnalka Szabó, MD, PhD
Hungary	Veszprem	Ferenc Csolnoky Hospital	Eva Szabo, MD Tamas Tenk, MD
Israel	Ashkelon	Barzilai University Medical Center	Shmuel Zangen, MD Mara Troitzky, MD
Israel	Beer Sheva	Soroka Medical Center	Kyla Marks, MD Eilon Shany, MD
Israel	Haifa	Bnai Zion Medical Center	Arieh Riskin, MD, PhD
Israel	Petah Tikva	Schneider Children's Medical Center	Raanan Shamir, MD, PhD Ruben Bromiker, MD Gil Klinger, MD

Israel	Haifa	Rambam Health Care Campus	Ori Hochwald, MD Huda Jubran, MD Naim Shehadeh, MD
Israel	Ramat Gan	Sheba Medical Center	Strauss Tzipora, MD, MSc Leibovitch Leah, MD
Israel	Tel Aviv	Tel Aviv Medical Center, Dana Dwek Children's Hospital	Dror Mandel, MD Alon Haham, MD
Italy	Ancona	AOU Ospedali Riuniti di Ancona	Virgilio P. Carnielli, MD, PhD Chiara Biagetti, MD Maria P. Bellagamba, MD
Italy	Milan	ASST FBF Sacco, Ospedale dei Bambini "V. Buzzi"	Gianluca Lista, MD, PhD
Italy	Milan	Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico	Paola Roggero, MD Orsola Amato, MD
Italy	Monza	MBBM Foundation, San Gerardo Hospital	Paolo Tagliabue, MD
Italy	Roma	Fondazione Policlinico Universitario A. Gemelli IRCCS - Università Cattolica del Sacro Cuore	Giovanni Vento, MD Simonetta Costa, MD
Italy	Varese	Ospedale Del Ponte, Università degli Studi dell'Insubria	Massimo Agosti, MD Laura Morlacchi, MD
The Netherlands	Amsterdam	Amsterdam University Medical Centers, Emma Children's Hospital	Elise Mank, MD Letty van Toledo, MD, PhD Johannes B. van Goudoever, MD, PhD
The Netherlands	Groningen	University Medical Center Groningen, Beatrix Children's Hospital	Elisabeth M.W. Kooi, MD, PhD Arend F. Bos, MD, PhD
The Netherlands	Zwolle	Isala	Richard A. van Lingen, MD, PhD Astrid Giezen, RN
Spain	Barcelona	Vall d'Hebron University Hospital	Felix Castillo, MD, PhD
Spain	Madrid	Hospital General Universitario Gregorio Marañón	Manuel Sánchez Luna, MD, PhD María del Carmen Sánchez Gómez de Orgaz, MD
Spain	Madrid	La Paz University Hospital	Miguel Sáenz de Pipaón, MD, PhD Marta Cabrera Lafuente, MD, PhD Esperanza Escribano, MD, PhD
Spain	Murcia	Virgen de la Arrixaca University Hospital	Manuel Cidrás, MD, PhD Macarena Quesada, PsyD
Spain	Santiago de Compostela	Complejo Hospitalario Universitario de Santiago	Maria L. Couce, MD, PhD Olalla López-Suárez, MD, PhD
Spain	Valencia	University and Polytechnic Hospital La Fe	Máximo Vento, MD, PhD María Gormaz, MD
United Kingdom	Bradford	Bradford Royal Infirmary	Sam Oddie, MBBS Rachel Wane, RN
United Kingdom	Leicester	University Hospitals of Leicester NHS Trust	Elaine M. Boyle, MD, PhD Marie Hubbard, MSc, RGN, RNCB
United Kingdom	Nottingham	Nottingham University Hospitals NHS Trust	Stephen P. Wardle MB, ChB, FRCPCH, MD Dushyant Batra, MD

United Kingdom	Portsmouth	Portsmouth Hospitals University NHS Trust	Tim Scorrer, MB, BCh Charlotte Groves, MBBS
United States	Nashville	Vanderbilt University Medical Center, Monroe Carell Jr. Children's Hospital	Joern-Hendrik Weitkamp, MD Theresa J. Rogers, RN
United States	Greenville	East Carolina University	Ryan T. Moore, MD, FAAP Devon Kuehn, MD
United States	Oklahoma City	University of Oklahoma College of Medicine	Kimberly D. Ernst, MD

eTable 2. Trial Steering Committee Members

Name	Institution	Country
Johannes B. van Goudoever MD, PhD (chair)	Amsterdam University Medical Centers, Emma Children's Hospital	The Netherlands
Miguel Sáenz de Pipáon, MD, PhD	La Paz University Hospital	Spain
Alexandre Lapillonne, MD, PhD	APHP Necker-Enfants Malades	France
Virgilio P. Carnielli, MD, PhD	AOU Ospedali Riuniti di Ancona	Italy
Thibault Senterre, MD, PhD	CHR de la Citadelle	Belgium

eTable 3. Enteral Nutrition Recommendation in the Study Protocol (ESPGHAN guidelines)⁽¹⁾

Birth weight (g)	Day 1*	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
<1000	0–20	0–30	15–35	20–35	32–48	48–72	65–95
≥1000	0–20	0–30	20–50	50–60	75–80	80–100	100–120

*Enteral nutrition in mL/kg/day

eTable 4. Total Fluid (Enteral and Parenteral) and Nutritive Components

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Total fluid (mL/kg/day)	60–100	80–120	80–140	100–140	120–170	120–170	120–170
Amino acids (g/kg/day)	1.5–2.5	2.5–3.5	3.0–4.0	3.0–4.0	3.0–4.5	3.0–4.5	3.0–4.5
Fatty acids (g/kg/day)	0.0–2.0	1.0–3.0	2.0–3.5	2.5–3.5	3.0–4.0	3.0–4.0	3.0–4.0
Glucose (g/kg/day)	5–10	8–10	10–12	11–13	11–13	11–13	11–13

eTable 5. Prespecified Sensitivity Analysis of the Primary Outcome*

	Low-dose rh-insulin (400 µIU/mL)	High-dose rh-insulin (2000 µIU/mL)	Placebo
Singletons and the first born sibling of a twin			
N	82	72	73
Median (IQR)	10.0 (7.0–21.8)	10.0 (6.0–15.8)	14.0 (8.0–28.0)
P-value ^{††}	0.12	0.01	–
Imputation of missing data			
N	110	95	98
Median (IQR)	10.0 (7.0–23.0)	10.0 (6.0–14.5)	14.5 (8.0–28.0)
P-value ^{††}	0.04	<0.001	–

*Primary outcome: time to achieve full enteral feeding (defined as an enteral intake ≥150 mL/kg/day for three consecutive days).

^{††}P-value represents comparison between the active-treatment group and the placebo group.

eReferences

1. Agostoni C, Buonocore G, Carnielli VP, et al. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. *J Pediatr Gastroenterol Nutr.* 2010;50(1):85-91.