

2. EXECUTIVE SUMMARY

Full Study Title: A Global Cross-sectional Survey to Capture Awareness and Knowledge of Mesenchymal Stem Cell (MSC) Therapy by Gastroenterologists and Colorectal Surgeons			
Phase:	Phase IV	Type:	Observational
Number of Subjects: 146 Physicians		Duration of Physician Participation: approximately 15 minutes	
Number of Study Centers: N/A		Duration of Study: 24 months	
Background and Rationale: Mesenchymal stem cells (MSC), otherwise known as mesenchymal stromal cells, are a heterogeneous group of stem cells characterized by multilineage differentiation, anti-inflammatory and immunomodulatory action, that are considered as a promising therapeutic option for treating inflammatory and autoimmune diseases. Recently the European Medicines Agency (EMA), the Israel and the Switzerland Regulatory Bodies approved Alofisel® (darvadstrocel), expanded human allogeneic MSCs extracted from adipose tissue, for the treatment of complex perianal fistulas in adult patients with nonactive/mildly active luminal Crohn’s disease (CD). In other indications, human MSCs have also been used in the treatment of graft-versus-host disease (GVHD), osteoarthritis, and further immune-mediated diseases, such as multiple sclerosis, systemic erythematous lupus, and nephropathies. There is a gap in the literature regarding the current knowledge, perception, awareness and perspectives of physicians who may be using or considering using MSC therapy. With the approval of Alofisel in Europe, Switzerland and Israel for the treatment of patients with complex perianal fistulas, this study aimed to understand this gap in the context of this indication. Observations generated from this survey may inform the development of medical education around Alofisel for gastroenterology specialists and coloproctologists/colorectal surgeons and ensure patient community awareness on progress in MSC therapy.			

Primary objective:

1. To quantitatively describe current perspectives, awareness and current knowledge state (including knowledge about mechanism of action) of MSC therapy amongst gastroenterologists and colorectal surgeons.

Secondary objectives:

The secondary objectives of the study were to quantitatively describe:

1. The sociodemographic and clinical experience characteristics of gastroenterologists and colorectal surgeons.
2. The level of awareness of MSCs amongst gastroenterologists and colorectal surgeons by type of institution.
3. The level of current knowledge state of MSCs amongst gastroenterologists and colorectal surgeons by type of institution.
4. The main concerns of gastroenterologists and colorectal surgeons related to MSC application and the types of information they would want to receive to alleviate these concerns.
5. Amongst gastroenterologists and colorectal surgeons who do not have concerns, the types of information that has alleviated these concerns.
6. By medical specialty (gastroenterologists and colorectal surgeons), the willingness to use MSC therapy in the clinical practice setting.

Exploratory objectives:

The exploratory objectives of the study were:

1. To quantitatively explore how factors (e.g. sociodemographic, clinical experience, information received) are associated with the awareness of MSCs.
2. To quantitatively explore how factors (e.g. sociodemographic, clinical

experience, information received) are associated with the current knowledge state of MSCs.
Study Design: Cross-sectional cohort study, assessed by means of a survey at one timepoint designed to describe current perspectives, awareness and knowledge of MSC therapy amongst gastroenterologists and colorectal surgeons.
Study Population: Study participants were gastroenterologists and colorectal surgeons identified using IQVIA's proprietary comprehensive database containing investigator specialty and contact details for physicians that are involved in research but also physicians not involved in research. In total, 387 gastroenterologists and colorectal surgeons were targeted to be enrolled in 15 countries¹. Sampling per country was weighted to reflect estimates of prevalence of CD per country and country population size and efforts were made to ensure recruitment from different sites and from each type of institution, to increase generalizability of findings. ○ Inclusion criteria: ▪ Physicians must be currently practicing registered gastroenterologists or colorectal surgeons and ▪ Physicians must be practicing within one of the in-scope countries ● Exclusion criteria ● There were no specific exclusion criteria for this survey.
Data sources and measurement: A study specific web/email survey was developed for use in this study. The survey included 37 questions (maximum of 33 effectively as a result of skipping patterns) including sociodemographic variables and variables related to the study outcomes and were expected to approximately 15 minutes to complete. It was developed following a hand search of literature identified by clinical members of the study team who are

¹ Israel, Germany, Denmark, Austria, Netherlands, Spain, Italy, Switzerland, France, United Kingdom, United States, Canada, Australia, Japan and South Korea.

familiar with MSC therapies and following a pragmatic literature review conducted to identify survey studies collecting physician perspectives in the broader stem cell field. In the majority of cases, data elements were collected via Qualtrics, the web-based survey platform, at a single timepoint.

In case a physician preferred to receive a copy of the questionnaire via email, data were collected in this format and uploaded into the electronic platform. For Japan, any paper versions of the survey completed in Japanese were uploaded into the electronic platform in English.

Data Management and Quality Assurance: All data elements were collected via Qualtrics, the web-based survey platform, at a single timepoint. In the event of missing or incoherent data in the web-based survey, the data management team contacted the physician to complete/clarify these data fields. Other steps in place to minimize missing data were included forcing responses to important variables used for addressing primary and secondary objectives, including response options to allow participants to opt out of responding where possible, autosaving the responses throughout survey completion, allowing the participant to save and return to the survey at a later time, including skip logic and response format validation and allowing survey completion on multiple modes of data collection (e.g. computer, smart device or paper).

Members of the research team located in each country were fully trained on using the online survey. Access to the online survey platform database was restricted with a username and password to members of the research team involved with the review of the completed surveys for completeness in order to contact the participating physicians with queries if needed.

Any identifying information has been removed from the database prior to database transfer for analysis purposes and therefore no identifying information were part of data analysis, reports, publications, or in any other disclosures, except where required by law.

Statistical Methods: All data processing, summarization, and analyses were performed using Statistical Analysis System (SAS) Enterprise Guide version 8.2 (SAS Institute, North Carolina).

Sample size

This study was intended to provide descriptive information; thus, a sample size of 387 physicians was considered to be a feasible and large enough sample to describe physician' perspectives, awareness and knowledge of MSC therapy per the primary objective, and the outcomes listed in the secondary objectives, and to explore these in a heterogeneous multinational sample.

In order to guarantee the precision to be less than 0.05 when the expected proportion is 0.5, which is the case of precision with the largest confidence interval, a sample size of 387 was chosen. This sample size would guarantee the precision to be less than 0.03 when the expected proportion is 0.1. Assuming a response rate of 20%, approximately 1,935 invitations were estimated to be sufficient to achieve the target sample size of 387 physicians.

The primary analysis was descriptive statistics for variables capturing current perspectives, awareness and current knowledge state of MSC therapy in the Full Analysis Set² (FAS) and Mesenchymal Awareness Set³ (MAS) populations.

Secondary analyses included descriptions of the following (in the FAS and MAS population):

- Sociodemographic and clinical experience characteristics,
- Awareness of MSCs by type of institution,
- Current knowledge state of MSCs by type of institution,

² including all enrolled gastroenterologists and colorectal surgeons who met all study inclusion criteria and none of the study exclusion criteria.

³ including all physicians from the FAS who reported at least limited awareness of MSC therapy (Q10).

- Awareness of MSCs by geographic region (Europe, Americas, Rest of World),
- Current knowledge state of MSCs by geographic region (Europe, Americas, Rest of World),
- Concerns of MSC application,
- Types of information physicians would want to receive to alleviate these concerns,
- Types of information physicians have received that has made them feel comfortable in physicians who have reported no concerns,
- Willingness to use MSC therapy in the clinical practice setting by medical specialty (gastroenterologists and colorectal surgeons).

Exploratory analyses consisted of the following (in the FAS population):

- Logistic regression models to explore the factors associated with awareness of MSCs,
- Logistic regression models to explore the factors associated with the current knowledge state of MSCs.

Results: In total 1,895 physicians were approached to complete the self-report MSC global survey. Among them, 253 physicians (13.4%) responded. In total, 148 physicians (7.8%) provided responses to the survey and 5.5% provided a response that they were did not want to participate. A total of 146 physicians made up the FAS population, after excluding 2 physicians with missing speciality information, and 115 made up the MAS population.

As per **secondary objective 1** physicians were mainly spread across Europe, most of them were aged at least 45 years old (45-54 years: 35.7%, $n=40$; +55 years: 40.2%, $n=45$), worked for an Academic Hospital (72.2%, $n=83$) or a District General Hospital (13.9%, $n=16$) and had been in practice for more than 10 years (11-20 years: 31.3%, $n=35$; >20 years: 59.8%, $n=67$). All the regions were predominantly represented by Gastroenterologists, and most Colorectal Surgeons (92.9%, $n=13$) were European.

❖ **Primary objective: Description of Physician Awareness, Knowledge and Perceptions of MSC Therapy**

In total, 22.6% ($n=26$) physicians from the MAS population reported ‘strong awareness’, 40.0% ($n=46$) reported ‘moderate awareness’ and 37.4% ($n=43$) reported ‘limited awareness’ of MSC therapy. In the FAS population, similar distribution was observed for the 3 previous categories, however 15.1% ($n=22$) also reported ‘heard of MSC therapy but do not know anything about it’ and 6.2% ($n=9$) reported ‘never heard of MSC therapy’ 18.8% ($n=21$).

Among physicians from the MAS population, 18.8% ($n=21$) reported having treated patients with MSC therapy and on average having treated 6.8 patients ($SD \pm 7.2$) in the past, and mainly reported having used adipose tissue as a source of MSC (81.0%, $n=17$). In addition, 53.2% ($n=58$) physicians reported that they kept themselves regularly up to date with developments in MSC field and mainly reported large interest (47.8%, $n=54$). ‘Immunomodulatory therapy’ (considered as the most appropriate term to describe MSC therapy) was reported by 33.7% ($n=35$) of the physicians, ‘immunomodulation’ (considered the appropriate term to describe the mechanism of action of MSC therapy for patients with CD and Complex Perianal Fistula [CPF]) was reported by 36.2% ($n=38$). Overall, just over a third of physicians reported having Familiar/Expert knowledge either of ‘MSC therapy in general’ or ‘mechanism of action of MSC therapy for patients with CD and CPF’ or ‘preparation and delivery process of MSC therapy for patients with CD and CPF’ and under half reported having Familiar/Expert knowledge either of ‘safety’ or ‘efficacy of MSC therapy for patients with CD and CPF’. Overall, it is important to note that 93.1% ($n=94$) of the physicians reported that MSC therapy is addressing an unmet need for CD patients with CPF, especially when [free-text response summary] the standard therapy failed (e.g. ‘failure to standard therapy’; ‘Refractory patients’), when no effective therapy exists (e.g. ‘a group of patients with no valid treatment alternative’; ‘difficult to treat’; ‘patients that are without an effective treatment now’) and also ‘patients with poor

quality of life’.

Regarding the sub-analyses by medical specialty (101 gastroenterologists and 14 colorectal surgeons); a descriptively larger proportion of Colorectal Surgeons reported ‘Moderate/Strong awareness’, ‘Familiar/Expert knowledge’, ‘Belief that MSC therapy addresses an unmet need for patients with CD and CPF’ than Gastroenterologists and a descriptively larger proportion of colorectal surgeons reported correct responses which required real knowledge of MSC therapy (e.g. mechanism of action, ‘Immunomodulatory therapy’, 50.0%, n=7 versus 31.1%, n=28) and more variability in responses choices were seen in the Gastroenterologists group.

Regarding the sub-analyses by region (68 Europeans; 16 Americans; 31 Rest of World); Overall, the proportion of physicians who reported having ‘Moderate/Strong awareness of MSC therapy’ (Europe: 70.6%, n=48; Americas: 25.0%, n=4; Rest of the World: 64.5%, n=20) or ‘Familiar/Expert knowledge of MSC therapy in general’ (Europe: 45.2%, n=28; Americas: 33.3%, n=4; Rest of the World: 19.4%, n=6) was descriptively higher in Europe than in the 2 other regions. Similar results were observed regarding the mechanism of action, delivery process, safety and efficacy knowledge of MSC therapy.

❖ **Secondary objective 2: The level of awareness of MSCs therapy by type of institution**

Most physicians in the MAS population reported working for an Academic Hospital (72.2%, n=83), and similar proportion reported working either for a District General Hospital (13.9%, n=16) or for ‘Other’ type of institution (13.9%, n=16). Similar proportions were observed in the FAS population. Overall, the proportion of physicians who reported ‘Strong awareness of MSC therapy’ (Academic Hospital: 26.5%, n=22; District General Hospital; 12.5%, n=2; Other: 12.5%, n=2); keeping themselves up to date with developments in MSC field was descriptively higher for those working in an Academic Hospital (Academic Hospital: 56.4%, n=44; District General Hospital: 43.8%, n=7; Other: 46.7%, n=7). Lastly, only physicians from Academic Hospital and District

General Hospital reported having ever-treated patients with MSC therapy (respectively 21.3%, [n=17] and 25.0% [n=4]).

❖ **Secondary objective 3: Current knowledge of MSCs amongst gastroenterologists and colorectal surgeons by type of institution**

Physicians in the MAS population from Academic Hospitals and District General Hospitals mainly reported that MSC therapy has approved indications for CPF in patients with CD. Even though most physicians from other institutions also reported this indication, a lower proportion was observed (Academic Hospital: 69.7%, n=53; District General Hospital: 66.7%, n=10; Other: 40.0%, n=6). The term ‘immunomodulatory therapy’ and ‘immunomodulation’ (respectively considered as the most appropriate term to describe MSC therapy and the Mechanism of action) were mostly reported by physicians from the District General Hospital (respectively 60.0%, n=9 and 46.7%, n=7). ‘Paracrine support for other cells’ (also considered a reasonable response to describe mechanism of action) was similarly reported by the physicians regardless of their institution (6.7% to 7.9%) and ‘Cell aid’ (also considered a reasonable response to describe mechanism of action) was only reported by one physician from Other institutions (7.1%, n=1). Lastly, a higher proportion of physicians from Academic Hospitals reported ‘Familiar/Expert’ knowledge of MSC therapy than physicians from the District General Hospital or those from Other institutions, whether in terms of efficacy (Academic Hospital: 53.9%, n=41; District General Hospital: 40.0%, n=6; Other: 35.7%, n=5), safety (Academic Hospital: 50.0%, n=38; District General Hospital: 33.3%, n=5; Other: 42.9%, n=6) and mechanism of action (Academic Hospital: 38.2%, n=29; District General Hospital: 26.7%, n=4; Other: 28.6%, n=4).

❖ **Secondary objective 4: Description of Physician Main Concerns of MSC Therapy and Information to Alleviate Concerns**

In the MAS population, 45.8% (n=49) of the physicians reported having concerns about

using MSC therapy to treat CD patients with CPF. Among these physicians, the most reported concerns were the 'Long-term efficacy' (63.8%, n=30), the 'Long-term safety' (51.1%, n=24) and the 'Cost effectiveness' (48.9%, n=23). These same concerns were ranked as more important by physicians. As ranked by physicians, the most important sources of information to alleviate concerns, were 'Peers/clinicians' ([First: 24.4%, n=11; Second: 24.4%, n=11; Third: 20.0%, n=9] and 'Medical/science associations' (First: 44.4%, n=20; Second: 15.6%, n=7; Third: 6.7%, n=3) and the most important types of information to alleviate concerns were 'published data from MSC clinical trials' (First: 76.1%, n=35; Second: 8.7%, n=4; Third: 4.3%, n=2) and 'published data from real-world studies' (First: 26.1%, n=12; Second: 45.7%, n=21; Third: 10.9%, n=5).

Regarding the sub-analyses by medical specialty; 'Cost', 'Mechanism of Action', 'Patient characteristics/Not applicable to certain patients' were reported by Colorectal surgeons at least 10% higher than the Gastroenterologists; 'No reimbursement/coverage in country', 'Worry due to lack of experience', 'Regulation', 'Infrastructure/lack of facilities', 'Ethical concerns' were reported by Gastroenterologists at least 10% higher than the Colorectal surgeon. The pattern of ranking responses generally followed a similar pattern to the reported concerns. Regarding the sub-analyses by region; 'Cost' and 'Lack of real-world evidence' were reported by European physicians at least 10% higher than the American and those from the Rest of the World. 'Cost effectiveness', 'Safety at administration', 'No reimbursement/coverage in country', 'Ethical concerns', 'Worry due to lack of experience', 'Regulation' and 'Short-term efficacy' were reported by American physicians at least 10% higher than the European and those from the Rest of the World.

Lastly 'Long-term efficacy' and 'Long-term safety' were always reported respectively first and second most important, whatever the region or medical specialty of physician. by medical specialty.

❖ **Secondary objective 5: Description of the Types of Information That Alleviated Concerns of MSC Therapy Amongst Physicians**

In the MAS population, 54.2% ($n=58$) of the physicians reported having no concerns about using MSC therapy to treat CD patients with CPF. As ranked by those physicians, the 3 most important sources of information that alleviated concerns were ‘Medical science associations’ (First: 37.3%; Second: 29.4%; Third: 9.8%), ‘Peers/clinicians’ (First: 23.5%; Second: 31.4%; Third: 19.6%) and ‘Industry/manufacturers’ (First: 33.3%; Second: 7.8%; Third: 17.6%) and the 3 most important type of information that alleviated concerns of MSC therapy were ‘Published data from MSC clinical trials’ (First: 67.3%; Second: 7.7%; Third: 7.7%), ‘Conference/congress presentations’ (First: 13.5%; Second: 40.4%; Third: 25.0%) and ‘Published data from real-world studies’ (First: 19.2%; Second: 23.1%; Third: 15.4%).

❖ **Secondary objective 6: Description of Physician Willingness to Use MSC Therapy in Clinical Practice**

In the MAS population, 82.4% ($n=89$) physicians reported willingness to use MSC therapy for CD patients with CPF in clinical practice. In the FAS population, 61.0% ($n=89$) of the physicians reported willingness to use MSC therapy for CD patients with CPF in clinical practice. Reasons related mainly to [free-text response summary] when previous treatments had failed, specific patient profiles (e.g. difficult to treat, severe, young patients), acknowledgement of positive efficacy/safety, or their actual experience of using it.

The proportion of physicians who reported willingness to use MSC therapy for CD patients with CPF in clinical practice were slightly lower amongst gastroenterologists (79.8%, $n=75$) than amongst colorectal surgeons (100.0%, $n=14$) and were highest in Europe (90.3%, $n=56$) followed by Rest of World (83.9, $n=26$) and were descriptively lower in the Americas (46.7%, $n=7$)

❖ **Exploratory objective 1: To quantitatively explore how factors (e.g. sociodemographic, clinical experience, information received) were associated with the awareness of MSCs**

Marginal associations or trends were observed between all predictors and the likelihood of reporting ‘strong’ or ‘moderate’ MSC awareness. After adjustment in the multivariable logistic regression model, only ‘attendance at any discussion or presentation on MSC therapy in last 2 years’ and the ‘Number of unique CD pts with CPF typically seen per year’ remained conditionally associated with MSC awareness.

❖ **Exploratory objective 2: To quantitatively explore how factors (e.g. sociodemographic, clinical experience, information received) were associated with the current knowledge of MSCs**

Marginal associations or trends were observed between all predictors and the likelihood of reporting ‘Familiar’ or ‘Expert’ MSC knowledge, except for ‘Type of institution’ ($p=0.5275$) and ‘Number of years practicing’ ($p=0.1899$). The planned multivariable model showed signs of model misfit and thus potentially biased estimates by the large number of variables compared to outcome events and the wide confidence intervals. A post-hoc model was thus conducted, removing MSC awareness as a predictor due to the very large effect and confidence interval, showed only ‘attendance at any discussion or presentation on MSC therapy in last 2 years’ and the ‘Number of unique CD pts with CPF typically seen per year’ remained conditionally associated with MSC knowledge.

Discussion and Conclusions: To the best of our knowledge, this is the first global study with the aim to describe the awareness, current knowledge, and perspectives of Gastroenterologists and Colorectal surgeons who may be using or considering using MSC therapies. A total of 148 physicians participated in survey - 146 physicians made up the FAS population and 115 made up the MAS population. They were mainly spread across Europe, most of them were aged at least 45 years old, worked for an Academic Hospital and had been

in practice for more than 10 years. All the regions were predominantly represented by Gastroenterologists, and most Colorectal Surgeons were European. Lastly Gastroenterologists reported seeing more CD patients and IBD patients per month than colorectal surgeons, however, the number of CD patients with CPF seen per year converged between the 2 medical specialties and may highlight that colorectal surgeons were a final link in the therapeutic management of CD patient with CPF.

❖ **Primary objective: Description of Physician Awareness, Knowledge and Perceptions of MSC Therapy:**

As no similar study of this type has been published in the scientific literature to the best of our knowledge, these findings are novel and cannot be related to previous findings. Nevertheless, this study suggests that there is a substantial proportion of gastroenterologists and colorectal surgeons who do not have strong or moderate awareness of MSC therapy. Physician's correct responses to knowledge questions (amongst incorrect answer choices) suggested that there is a large lack of understanding amongst gastroenterologists and colorectal surgeons about what MSC therapy is and how it works. This was observed by the most prevalent answer choices being 'tissue engineering' (41.3%) and 'cell engraftment' for MSC mechanism of action (37.1%) suggesting this lack of understanding. The proportions of physicians providing correct responses were consistent with the physicians who reported having Familiar/Expert knowledge of MSC therapy: about third of them reported Familiar/Expert knowledge of MSC therapy, and similar findings were observed for those who reported the most appropriate term to describe MSC therapy and the mechanism of action. Considering the observed magnitude of incorrect knowledge responses and self-perceived knowledge, this finding suggests the necessity for further educating physicians in the field. Concerning perceptions of MSC therapy, the vast majority of the physicians (93.1%) reported that MSC therapy does address an unmet need, suggesting that even physicians with limited awareness or knowledge had a belief of the potential of MSC therapy. Furthermore, physicians indicated in their own words that MSC therapy meets an unmet need in patients

for whom standard therapy has failed or for whom there is no current effective therapy; especially concerning difficult to treat and severe patients and patients with poor quality of life.

Regarding the sub-analyses by medical specialty (101 gastroenterologists and 14 colorectal surgeons) and by region (68 Europeans; 16 Americans; 31 Rest of World) the different sub-population necessitate cautionary interpretation within the smaller subgroups. Overall, colorectal surgeons' responses showed a general trend of increased awareness/knowledge/perception of MSC therapy than gastroenterologists and European physicians showed an increased awareness/knowledge/perception of MSC therapy than Americas and those from the Rest of the World. This may reflect an increased knowledge in Europe; however, it may be also be at least partially attributable to the approval of Alofisel only in Europe, Switzerland, and Israel at time of study conduct. Lastly, whatever their region, similar proportions of physicians believed that MSC therapy is addressing an unmet need.

❖ **Secondary objective 2: The level of awareness of MSCs therapy by type of institution:**

There was no conclusive trend difference in awareness between physicians in Academic Hospitals compared to District General Hospitals, although both of these groups appeared to have higher awareness compared to in physicians from other institutions.

❖ **Secondary objective 3: Current knowledge of MSCs amongst physicians by type of institution:**

Although physicians from Academic Institutions or District General Hospitals appeared to report grater knowledge of MSCs than those from other institutions, it seems difficult to descriptively conclude about any knowledge differences between these 2 types of institutions (Academic Institutions and District General Hospitals). Lastly, although the vast majority of physicians reported that MSC therapy addresses an unmet need for patients with CD and CPF, the proportion was larger in those working in Academic Hospitals.

❖ **Secondary objective 4: Description of Physician Main Concerns of MSC Therapy**

and Information to Alleviate Concerns: Just under half of physicians who at least heard of MSC therapy (MAS population) reported having concerns about using MSC therapy (45.8%). The most important concerns reported by physicians were consistently related to ‘Long-term efficacy’, ‘Long-term safety’ and economic issues (cost and cost effectiveness) and safety at administration. Independently, these observations provide evidence to the extent of self-perceived concerns and main areas of concern, but do not indicate whether concerns relate to areas of perceived inadequacy of MSC therapy (e.g. “inadequate long-term efficacy”) or lack of knowledge or understanding (e.g. “insufficient understanding of long-term efficacy”). The most important sources of information to alleviate concerns were ‘Peers/clinicians’, ‘Medical/science associations’, and ‘Industry manufacturers’ and the most important types of information to alleviate concerns were ‘Published data from MSC clinical trials’, ‘Published data from real-world studies’, and ‘Conference/congress presentations’. Although ‘Long-term efficacy’ and ‘Long-term safety’ were always reported respectively the first and second most important, whatever the region or medical specialty of physician, sub-analyses made it possible to distinguish minor descriptive differences.

❖ **Secondary objective 5: Description of the Types of Information That Alleviated**

Concerns of MSC Therapy Amongst Physicians: Just over half of physicians who at least heard of MSC therapy (MAS population) reported having no concerns about using MSC therapy (54.2%). Whatever the physician’s medical specialty or region, ‘Medical science associations’, ‘Peers/Clinicians’, and ‘Industry manufacturers’ were consistently reported as main source of information to alleviate concerns and a consensus was seen regarding the “published data from MSC clinical trials” which was the most reported type of information reported by physician, regardless of their region or medical specialty.

❖ **Secondary objective 6: Description of Physician Willingness to Use MSC Therapy in**

Clinical Practice: Overall, physicians were overwhelmingly willing to use MSC therapy

for CD patients with CPF, although gastroenterologists appeared less willing than colorectal surgeons, as were physicians in the Americas subgroup, where less than half reported being willing to use MSC therapy for CD patients with CPF. This reduced willingness in the Americas subgroup is likely attributable to the non-approved status of Alofisel in this region at time this study was conducted. The main justifications physicians provided in their own words were centred around the ‘unmet need for patients when the standard therapy failed’, specific patient profiles (e.g. young, severe, difficult to treat, refractory patients) the positive efficacy/safety in clinical trials and their actual experiences of using MSC therapy.

❖ **Exploratory objective 1 and 2:** Marginal associations between almost all predictors and the likelihood of reporting ‘strong’ or ‘moderate’ MSC awareness and ‘Familiar’ or ‘Expert’ MSC knowledge were observed in the univariable models and all associations showed intuitive directionality (e.g. likelihood of strong/moderate awareness in the Americas group compared to the European group; higher MSC awareness and knowledge of Colorectal Surgeons compared to gastroenterologist; factors generally associated with increased experience all showed marginal associations with MSC awareness or knowledge). Regarding the multivariable logistic regression models, only the ‘attendance at any discussion or presentation on MSC therapy in last 2 years’ and the ‘Number of unique CD pts with CPF typically seen per year’ remained conditionally associated with MSC awareness and knowledge.

Limitations: This study had a number of limitations as follows:

- Due to the real-world nature of the data and the descriptive purposes of the study objectives, some study variables were missing and not imputed. However, this allowed physicians who are unsure or prefer not to respond to do so, which minimizes physicians reporting inconsistently just for the purpose of completing the survey.
- The sample size was lower than expected and many of this study’s objectives were

based on subgroup analyses with sample size that varied substantially by categories. The generalizability of this study's findings was thus limited in subgroups of small sample size and had an impact on the variability around the sample proportions in the region compared to the planned sample size. The smaller sample size also impacted the statistical power of the logistic regression models to detect associations with MSC awareness and knowledge in accordance with exploratory objectives 1 and 2.

- The recruitment process occurred during the ongoing pandemic situation due to the COVID-19, which may have impacted physicians' willingness to participate in this type of study
- Physicians did not receive any compensation for their time, which may explain, to some extent, the lower response rates (13.3%; 1,895 physicians were approached and only 253 physicians responded). Future studies should consider issuing compensation to physicians in order to try to increase representation of physicians who would normally not be interested in participating in a research study if it is in a topic that is not of interest to them.
- Due to local hospital regulation changes due to the ongoing COVID-19 pandemic, it is likely that physicians may have seen fewer patients per month and may have had less time to involve themselves in scientific activities around MSC therapy, thus these estimates may be underestimated in our sample.
- Physicians were recruited by a panel (for all countries) and were selected to complete the survey based on their eligibility as a Colorectal surgeons or Gastroenterologists specialist. Importantly, all physicians answered the same survey questions. There were no differences in the questionnaires, outside of translation.

Conclusion: Overall, there is a need to improve the awareness, current knowledge and perspectives of physicians who may be using or considering using MSC therapies. Our findings indicate that in Colorectal surgeons and Gastroenterologists who have some

awareness of MSC therapy, there is a high interest and willingness to use MSC therapy and belief that it meets an unmet need. Despite this, a substantial proportion of physicians do not have strong or moderate awareness and enough knowledge of MSC therapy. Therefore, further communication and education are encouraged to support physicians in their decision making and adoption of MSC therapy. By identifying the main types and sources of information that have alleviated concerns about using MSC therapy and key areas of concerns, overall and by physicians' medical specialty, region or type of institution, actions may be initiated accordingly to accelerate understanding and use of this innovative therapy.

Ethical and Regulatory Considerations: Consistent with local regulations and prior to enrolment of physicians, the study protocol was submitted with the physician survey to the responsible IRB/ independent ethics committee (IEC), the New England Institutional Review Board (NEIRB) and approval was received April 10th, 2020. In accordance with local regulations and the ethical principles that have their origin in the principles of the Declaration of Helsinki, all physicians provided agreement to a data protection notice (DPN) or website cookie policy electronically before entering into the study. Physician agreement to a DPN or cookie policy were obtained prior to being granted access to the survey. By agreeing to the DPN or cookie policy, the physician consented to their data being used in the study unless they withdraw voluntarily afterwards for any reason. As physicians were not compensated for participating in this study, S.301 – Physician Payments Sunshine Act of 2009 is not applicable.